DOCKET

SUPREME COURT
OF THE UNITED STATES

No. 10-1150
Title: Mayo Collaborative Services dba Mayo Medical Laboratories, et al., Petitioners
v.
Prometheus Laboratories, Inc.
Docketed: March 21, 2011
Lower Ct: United States Court of Appeals for the Federal Circuit
Case Nos.: (2008-1403)
Decision Date: December 17, 2010
Questions Presented:

~~Date~~~	~~~~~~~~Proceedings and Orders~~~~~~~~~~~~~~~~~~~~~
Mar 17 2011	Petition for a writ of certiorari filed. (Response due April 20, 2011)
Apr 13 2011	Order extending time to file response to petition to and including May 20, 2011.
Apr 20 2011	Brief amici curiae of American College of Medical Genetics, et al. filed.
Apr 20 2011	Brief amici curiae of AARP, and Public Patent Foundation filed.
May 20 2011	Brief of respondent Prometheus Laboratories, Inc. in opposition filed.
May 31 2011	Reply of petitioner Mayo Collaborative Services filed.
May 31 2011	DISTRIBUTED for Conference of June 16, 2011.
Jun 20 2011	Petition GRANTED.
Jul 13 2011	The time to file the joint appendix and petitioners' brief on the merits is extended to and including September 2, 2011.
Jul 13 2011	The time to file respondent's brief on the merits is extended to and including October 31, 2011.
Aug 4 2011	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for the respondent.
Aug 5 2011	Letter from counsel for the petitioners proposing to lodge chapter page proofs of to be published book.
Aug 8 2011	Consent to the filing of amicus curiae briefs, in support of either party or of neither party, received from counsel for the petitioners.
Sep 2 2011	Brief of petitioners Mayo Collaborative Services and Mayo Clinic Rochester filed.
Sep 2 2011	Joint appendix filed (two volumes). (Statement of costs received)
Sep 6 2011	Brief amici curiae of Association Internationale pour la Protection de la Propriete Intellectuelle, et al. in support of neither party filed.
Sep 8 2011	Brief amicus curiae of New York Intellectual Property Law Association in support of neither party filed.
Sep 8 2011	Brief amicus curiae of American Civil Liberties Union filed.

Sep 9 2011	Brief amicus curiae of the United States in support of neither party filed.
Sep 9 2011	Brief amici curiae of Verizon Communications Inc. and Hewlett-Packard Company filed.
Sep 9 2011	Brief amici curiae of Microsoft Corporation, et al. in support of neither party filed.
Sep 9 2011	Brief amici curiae of AARP and Public Patent Foundation filed.
Sep 9 2011	Brief amicus curiae of Cato Institute, et al. filed.
Sep 9 2011	Brief amici curiae of American College of Medical Genetics, et al. filed.
Sep 9 2011	Brief amici curiae of ARUP Laboratories, Inc., et al. filed.
Sep 9 2011	Brief amici curiae of Nine Law Professors filed.
Sep 9 2011	Brief amici curiae of Roche Molecular Systems, Inc., et al. filed.
Sep 12 2011	SET FOR ARGUMENT ON Wednesday, December 7, 2011.
Sep 19 2011	CIRCULATED
Sep 26 2011	Record received from U.S.C.A. for Federal Circuit. (1 box)
Oct 4 2011	Record received from U.S.D.C. for Southern District of California. (1 box). This record contains sealed documents.
Oct 26 2011	Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument filed.
Oct 31 2011	Brief of respondent Prometheus Laboratories, Inc. filed. (Distributed)
Nov 1 2011	Brief amicus curiae of The Juhasz Law Firm, P.C. filed. (Distributed)
Nov 2 2011	Brief amicus curiae of Intellectual Property Owners Association filed. (Distributed)
Nov 7 2011	Brief amici curiae of SAP America, Inc. filed. (Distributed)
Nov 7 2011	Brief amicus curiae of American Intellectual Property Law Association filed. (Distributed)
Nov 7 2011	Brief amicus curiae of Pharmaceutical Research and Manufacturers of America filed. (Distributed)
Nov 7 2011	Brief amicus curiae of Association of University Technology Managers filed. (Distributed)
Nov 7 2011	Brief amicus curiae of Myriad Genetics, Inc. filed. (Distributed)
Nov 7 2011	Brief amicus curiae of Biotechnology Industry Organization filed. (Distributed)
Nov 7 2011	Brief amicus curiae of Novartis Corporation filed. (Distributed)
Nov 7 2011	Brief amici curiae of Genomic Health, Inc., et al. filed. (Distributed)
Nov 7 2011	Brief amicus curiae of Intellectual Property Law Association of Chicago filed. (Distributed)
Nov 7 2011	Brief amicus curiae of Intellectual Property Amicus Brief Clinic of the University of New Hampshire School of Law filed. (Distributed)
Nov 7 2011	Brief amici curiae of Health Law, Policy, and Ethics Scholars filed. (Distributed)
Nov 7 2011	Brief amicus curiae of National Venture Capital Association filed. (Distributed)
Nov 7 2011	Brief amici curiae of CONNECT, and San Diego Intellectual Property Law Association filed. (Distributed)
Nov 15 2011	Reply of petitioners Mayo Collaborative Services, et al. filed. (Distributed)
Nov 22 2011	Motion of the Solicitor General for leave to participate in oral argument as amicus curiae and for divided argument GRANTED.
Dec 6 2011	Letter from counsel for respondent filed. (Distributed)
Dec 7 2011	Argued. For petitioners: Stephen M. Shapiro, Chicago, ILL. For United States as amicus curiae: Donald B. Verrilli, Jr., Solicitor General, Department of Justice, Washington, D. C. For respondent: Richard P. Bress, Washington, D. C.
Mar 20 2012	Judgment REVERSED. Breyer, J., delivered the opinion for a unanimous Court.

PETITION FOR WRIT OF CERTIORARI

No. 10-

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

This case concerns whether a patentee can monopolize basic, natural biological relationships. The Court has twice granted certiorari on the question presented, without yet resolving the issue. Last year, it granted certiorari, vacated, and remanded in this case to allow the Federal Circuit to reconsider this question in light of *Bilski* v. *Kappos*, 130 S. Ct. 3218 (2010). And seven years ago it granted certiorari but dismissed the writ as improvidently granted in *Laboratory Corp. of America Holdings* v. *Metabolite Laboratories, Inc.*, 548 U.S. 124, 135 (2006), because petitioner there had not adequately preserved the question.

The question presented is:

Whether 35 U.S.C. § 101 is satisfied by a patent claim that covers observed correlations between blood test results and patient health, so that the claim effectively preempts all uses of the naturally occurring correlations, simply because well-known methods used to administer prescription drugs and test blood may involve "transformations" of body chemistry.

RULES 14.1(b) AND 29.6 STATEMENT

All parties are identified in the caption of this petition. Petitioner Mayo Collaborative Services, a subsidiary of Mayo Clinic, is a for-profit Minnesota corporation that provides reference laboratory services under the name Mayo Medical Laboratories. Petitioner Mayo Clinic Rochester, a subsidiary of Mayo Clinic, is a charitable, nonprofit corporation located in Rochester, Minnesota. No publicly held company owns 10% or more of the stock of either petitioner.

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PETITION FOR A WRIT OF CERTIORARI

Petitioners, Mayo Collaborative Services (d/b/a Mayo Medical Laboratories) and Mayo Clinic Rochester (collectively, "Mayo"), respectfully petition for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS BELOW

The Federal Circuit's opinion following remand from this Court (App., *infra*, 1a-23a) is reported at 628 F.3d 1347 (Fed. Cir. 2010). This Court's order granting certiorari, vacating, and remanding in light of *Bilski* v. *Kappos* (App., *infra*, 24a) is reported at 130 S. Ct. 3543 (2010). The Federal Circuit's original opinion (App., *infra*, 25a-49a) is reported at 581 F.3d 1336 (Fed. Cir. 2009). The district court's opinion holding Prometheus's patents invalid (App., *infra*, 50a-83a) is reported at 2008 WL 878910 (S.D. Cal. Mar. 28, 2008).

JURISDICTION

The court of appeals entered its judgment on December 17, 2010. This petition is filed within 90 days of that judgment. The jurisdiction of this Court is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101.

"The term 'process' means process, art or method, and includes a new use of a known process, machine,

manufacture, composition of matter, or material." 35 U.S.C. § 100(b).

INTRODUCTION

The issue presented in this case is one of exceptional importance in the healthcare and life science fields that affects patients across the Nation. Simply put, Prometheus's patents monopolize every useful implementation of a correlation between particular types of drug treatment and the natural bodily metabolism resulting from that drug treatment. This correlation is unquestionably a natural phenomenon. From it, doctors may determine if a dose of a drug is too high, too low, or needs no adjustment at all. But if Prometheus's patents are allowed to stand, doctors will no longer be free to consider this biological phenomenon in treating patients or in attempting to develop new treatments for disease. And numerous similar, overly-broad patents that restrict doctors' ability to treat patients will stand as well. This will stifle innovation, as well as raise the cost and degrade the quality of medical care throughout the United States.

This Court previously recognized the importance of the issue when it granted certiorari in *Laboratory Corp. of America Holdings* v. *Metabolite Laboratories, Inc.*, 548 U.S. 124, 135 (2006) ("*LabCorp*"). The Court could not resolve the merits there because a majority did not believe that the *LabCorp* petitioner adequately preserved the issue. But three dissenting Justices would have decided the case. In their dissent, they pointed out the great public importance of the issue and explained that the *LabCorp* patent claims—which are not materially different from Prometheus's claims here—were not even "at the boundary" of patentability.

The district court here reached the same conclusion, finding in a detailed opinion that Prometheus's claims were invalid because they "wholly pre-empt" natural correlations. App., *infra*, 75a-78a. But the Federal Circuit reached the opposite conclusion—both before this Court's decision in *Bilski* v. *Kappos*, 130 S. Ct. 3218 (2010), and after vacatur and remand—while twice declining even to consider *LabCorp*.

Before *Bilski*, the Federal Circuit applied its own "machine or transformation" test as a "definitive" standard under Section 101—a position this Court rejected in *Bilski*. But even though *Bilski* affirmed the primacy of a "preemption" analysis, the Federal Circuit on remand again mechanically applied its "machine or transformation" test, and it again "decline[d] to discuss" the reasoning of Justices Breyer, Stevens, and Souter in *LabCorp*. Even though Prometheus's patent claims merely recite a physician's mental recognition of a correlation between a patient's health and blood levels of metabolites after administration of a drug, the Federal Circuit held that such a correlation may be patented because the steps needed to elicit the correlation involve "transformations" of the human body. But these steps are simply the administration of the drug and the measurement of metabolite levels, both of which had been known in the art for decades. This was enough for the Federal Circuit to find patent-eligibility for a process that—far from constituting any innovation—is nothing more than the body's natural reaction to the ingestion of drugs, and a mental recognition of that natural reaction.

The Federal Circuit's decision is inconsistent with this Court's earlier precedents, with the reason-

ing of three Justices in *LabCorp*, and with *Bilski*. The *Bilski* Court recognized that the "preemption" standard controls Section 101 decisions. 130 S. Ct. at 3229-3231. Prometheus's claims broadly monopolize all uses of physician-recognized natural correlations —failing the preemption standard even if natural "transformations" of body chemistry may lead up to those correlations.

As reflected in the grant of certiorari in *LabCorp* and the host of amicus filings in that case, the question presented is one of extraordinary public importance. Justices Breyer, Stevens, and Souter explained in *LabCorp* that "special public interest considerations" are implicated by the question presented because overbroad patents will "inhibit doctors from using their best medical judgment," "force doctors to spend unnecessary time and energy to enter into license agreements," "divert resources" from healthcare tasks to "the legal task of searching patent files," and "raise the cost of healthcare while inhibiting its effective delivery." 548 U.S. at 138. Even more so today—with rising national concerns over healthcare quality and cost—these considerations warrant this Court's review, which may now proceed without the preservation problems that prevented resolution in *LabCorp*.

STATEMENT

A. Prometheus's Sweeping Patent Claims.

Prometheus's broad patent claims attempt to turn a physician's thought processes into infringement.[1] Specifically, these claims encompass a physi-

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[1] U.S. Patents 6,355,623 ("the '623 patent") and 6,680,302 ("the '302 patent"), reproduced at C.A. App. A10001 and A10019, are

cian's mental determinations when evaluating a patient who has been given a thiopurine drug, a kind of drug that was discovered over 30 years ago. Enzymes in the human body convert such drugs naturally into metabolites. App., *infra*, 65a. Low levels of such metabolites indicate an insufficient dose of the drug, and high levels indicate too much. Physicians understood these facts well before Prometheus filed its patent claims, as conceded in those claims.[2]

What the Prometheus patents purport to add is a recognition that *particular metabolite levels* are relevant to proper drug dosages for a variety of autoimmune disorders. App., *infra*, 2a-4a; '623 Patent at 8:40-46, C.A. App. A10010. Those correlations already existed in the studied patient population. Prometheus simply analyzed patient data assembled by other parties to "discover" the levels it claimed were relevant. App., *infra*, 65a-66a; C.A. App. A12833-12836, A13330-13331. For many years previously, doctors considered metabolite levels and made their own independent judgments about them—whether they were too high, too low, or just right. See n.2, *supra*.

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also available at http://tiny.cc/y867p and http://tiny.cc/TR2FY, respectively.

[2] See, *e.g.*, '623 Patent at 8:37-39, C.A. App. A10010 (citing "[p]revious studies" that concluded "measurement of 6-MP metabolic levels can be used to predict clinical efficacy and tolerance" to thiopurine drugs); '623 Patent at 9:13-14, C.A. App. A10011 (relevant metabolite levels "can be determined by methods well known in the art"); C.A. App. A12698-12701, A12705-12712, A12714-12718 (scientific papers from 1982-1990 describing tests for relevant metabolite of thiopurine); *id.* at A12722-12727 (1989 article discussing "acute thiopurine toxicity"); *id.* at A12842-12844 (conceding prior testing for thiopurine metabolites).

Claim 1 of the '623 patent, for example, has just two basic steps: (a) administering some indefinite amount of the drug to the patient, and then (b) considering whether that test dosage was too little, just right, or too much to treat the patient based on observed metabolite levels (known as 6-thioguanine (6-TG)):

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per 8x108 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per 8x108 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

C.A. App. A10016; see App., *infra*, 3a-5a (describing patent claims at issue). Other claims, such as claim 46 of the '623 patent, do not even require the "administering" step—and thus recite only the step of "determining." See App., *infra*, 4a-5a.

Importantly, Prometheus's claims do *not* recite what is to be done once the physician mentally re-

cognizes the correlation. App., *infra*, 60a-62a. The claims therefore cover and preempt *all* uses of the natural correlation. What the physician might do with her observation is irrelevant because simply thinking about the subject completes the act of infringement. As Prometheus's expert testified, if a physician reads an email with the test results, it would not matter if she "crumples it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with." C.A. App. A13557-613558; see also C.A. Supp. App. A13805-13806. The physician infringes the moment she thinks or thinks again about the correlation, regardless of what she intends to do with the information or whether she acts upon it.

Notably, infringement occurs even when the dose of drug administered to a patient is a test dose and not a dose intended to treat the patient, because the claims do not specify the proper size of the dose but merely recite the mental recognition of metabolite levels that are too low or too high. The Federal Circuit's analysis, however, relies centrally on a supposition that the claims—even the claims that do not recite administration of any drug to the patient—are patent-eligible because they describe patient *treatment*. App., *infra*, 15a-18a. The falsity of that supposition goes to the core of this case. Prometheus's failure to claim any particular real-world use of the natural laws on which its claims rely—its failure to recite a particular treatment or anything else—causes the claims to preempt all such uses of the physician-recognized natural correlations.

Mayo argued in the district court in favor of a narrow interpretation of these patent claims that would require some real-world action, such as requir-

ing the doctor to adjust the amount of drug given to the patient. C.A. App. A12245-12249. But Prometheus opposed that position. It successfully argued that a physician only had to identify a potential need to adjust dosage—and nothing else—to infringe. The district court agreed with Prometheus that its patents were this broad. See App., *infra*, 107a-110a.

Prometheus's infringement accusations against Mayo researcher Dr. Rokea el-Azhary highlight the extraordinary breadth of these patents. Dr. el-Azhary is a dermatologist. She gave her dermatological patients a thiopurine drug to try to establish a therapeutic range for skin disorders. See C.A. App. A12846. But because the lab report she received referred to the correlation ranges in Prometheus's claims, Prometheus accused her of infringement:

> The Biochemical Genetics Laboratory at Mayo Clinic Rochester sent a report of test results to Dr. El-Azhary, or someone working for Dr. el-Azhary. The test results described the "therapeutic range" as "235-400." The Biochemical Genetics Laboratory at Mayo Clinic Rochester did not subsequently advise Dr. el-Azhary that the "therapeutic range" was not "235-400."
>
> Such information informed Dr. el-Azhary, or someone working for Dr. el-Azhary (and thus "indicated a need"), that the next dose of azathioprene given to the patient should be increased in order to be within the "therapeutic range."

C.A. App. A12788; A12821-12822. Prometheus even asserted infringement when Dr. el-Azhary subsequently received reports that did not list the "thera-

peutic range"—on the ground that the ranges were still in her memory. *Id.* at A12853-12854 ¶ 5.

Dr. el-Azhary testified that she knew the numbers, but because Prometheus's range was developed from patients with gastrointestinal disorders, it was "irrelevant to [her] study" of metabolite levels in patients with dermatological disorders. C.A. App. A12848-12850. Under Prometheus's patents, Dr. el-Azhary must stop her dermatological research until she rids her memory of the gastrointestinal correlations—regardless of how she ultimately may use any test results—because Prometheus's patents preempt all possible uses of the correlations. If these claims are allowed to stand, Prometheus can sue anyone who thinks about the claimed correlations when conducting research or treating patients, no matter how they obtain such information—including by reading this petition.

B. The District Court's Decision Invalidating The Patents.

Prometheus sued Mayo in 2004 over a test that Mayo developed to measure metabolites in patients treated with thiopurine drugs. Mayo's proposed test did not use the ranges from Prometheus's patent claims. App., *infra*, 85a. After construing the claims broadly, the district court granted Prometheus summary judgment and held that the claims were infringed. *Id.* at 110a-116a. Mayo then moved for summary judgment that Prometheus's claims were invalid under 35 U.S.C. § 101, and the court granted Mayo's motion. See App., *infra*, 52a-54a (describing procedural history).

The district court relied on this Court's case law deeming patent claims invalid if they wholly preempt

all uses of a natural phenomenon or abstract idea. App., *infra*, 60a-63a, 66a, 72a-78a. The court first noted that the Prometheus claims recite correlations between thiopurine drug metabolite levels and therapeutic efficacy or toxicity. *Id.* at 62a-63a. The court rejected, as form over substance, Prometheus's argument that the claims recite "methods" rather than natural phenomena. Looking at the steps of the claims, the court explained that the steps reciting "administering" a drug and "determining" metabolite levels were mere data-gathering steps that were necessary precursors for reviewing the claimed correlations. *Id.* at 63a. In summarizing the claims, the court noted: "what the inventors claim to have discovered is that particular concentrations of [thiopurine metabolites] correlate with therapeutic efficacy and toxicity in patients taking AZA drugs." *Ibid.*

The court then held that the correlations are natural phenomena. Rejecting Prometheus's argument that the correlations could not be natural because thiopurine is a synthetic drug, the court observed that Prometheus's claims are directed to the correlations and not to the making of the drug. Prometheus's expert admitted that "the key therapeutic aspect of such thiopurine drugs is that they are converted naturally by enzymes within the patient's body to form an agent that is therapeutically active." App., *infra*, 65a. Prometheus also admitted that the testing and correlations already existed in a "database of patient's information," and that the correlations likely still exist in the current patient population. *Ibid.* As a result, the court (*id.* at 66a) concluded that Prometheus

> did not "create" the correlation between thiopurine drug metabolite levels and therapeutic efficacy and toxicity. Instead, the correlation results from a natural body process, which as the inventors concede, was preexisting in the patient population, and it exists in the patient population today.

In analyzing Prometheus's claim, the district court found instructive the *LabCorp* opinion of Justices Breyer, Stevens, and Souter, which, citing this Court's precedents, explained that the similar claim there failed "the requirement that it not amount to a simple natural correlation, *i.e.*, a 'natural phenomenon'":

> At most, respondents have simply described the natural law at issue in the abstract patent language of a "process." But they cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge. One might, of course, reduce the "process" to a series of steps, *e.g.*, Step 1: gather data; Step 2: read a number; Step 3: compare the number with the norm; Step 4: act accordingly. But one can reduce *any* process to a series of steps. The question is what those steps embody. And here, aside from the unpatented test, they embody only the correlation between homocysteine and vitamin deficiency that the researchers uncovered. In my view, that correlation is an unpatentable "natural phenomenon," and I can find nothing in [the claim] that adds anything more of significance.

LabCorp, 548 U.S. at 137-138 (citation omitted), quoted at App., *infra*, 67a-68a.

The district court then concluded that the Prometheus claims preempt a natural phenomenon under this Court's precedents. It noted that this Court's preemption standard in *Gottshalk* v. *Benson*, 409 U.S. 63 (1972), and *Parker* v. *Flook*, 437 U.S. 584 (1978), governs, and not a "transformation" test. App., *infra*, 72a-74a. And it explained that Prometheus's sweeping claims improperly preempt all uses of these correlations, because every activity recited in the claims other than recognition of the correlations was simply data gathering necessary to observe the natural correlations (*id.* at 75a-78a):

> what the inventors claim to have discovered is that particular concentrations of 6-TG and 6-MMP correlate with therapeutic efficacy and/or toxicity in patients taking AZA drugs. Because the claims cover the correlations themselves, it follows that the claims "wholly pre-empt" the correlations.

C. The Federal Circuit's First Decision Upholding The Patents, And This Court's Post-*Bilski* Vacation Order.

The Federal Circuit reversed. It applied its own "machine or transformation" test as a "definitive" standard, and glossed over Justice Breyer's *LabCorp* opinion in a footnote. See App., *infra*, 33a-34a, 40a n.3. Prometheus invited that ruling by insisting in its briefing that "a freestanding preemption inquiry is inappropriate" because "*Bilski's* 'machine or transformation test is the singular test for a process claim under § 101.'" Prometheus Reply Br. 21 n.3 (Fed. Cir. Apr. 24, 2009).

In a petition for certiorari that was supported by numerous amici,[3] Mayo argued that the Federal Circuit erred by elevating the "machine or transformation" test over this Court's holdings that require analysis of a patent claim's preemption of the use of natural phenomena. Mayo Pet., No. 09-490, at 13. Mayo showed (at 14-19) that because the Prometheus claims do not say what is to be done with a doctor's recognition of the natural correlations they recite, they cover all uses and thus improperly preempt them. Amici emphasized that attempted patenting of medical correlations "has led to severe restraint on the provision of medical care and a greatly increased cost and reduced availability of vital medical services" (Am. Br. of AARP, *et al.*, No. 09-490, at 4); that interference with physicians' mental processes raises ethical concerns and erodes physicians' ability to provide quality care (Am. Br. of American College of Medical Genetics, *et al.*, at 9-11); and the Federal Circuit's holding lets companies claim ownership of matter that is already in the public's "storehouse of knowledge." Am. Br. of Quest Diagnostics, *et al.*, at 5. For its part, Prometheus asserted in its brief in opposition (at 24-26) that "machine or transformation" was the definitive standard.

While the petition was pending, this Court decided *Bilski* v. *Kappos*. Though *Bilski* included three opinions, all agreed on a number of key points. First,

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[3] AARP, the Public Patent Foundation, the American College of Medical Genetics, the American Society of Human Genetics, the Association of Professors of Human and Medical Genetics, the Association for Molecular Pathology, the College of American Pathologists, Quest Diagnostics Inc., Laboratory Corporation of America Holdings, Arup Laboratories, Inc., and Tricore Reference Laboratories.

they disapproved of the Federal Circuit's rote reliance on "machine or transformation" as the standard for patent eligibility, and demanded a more nuanced inquiry. Each opinion also affirmed that natural phenomena and abstract ideas lie outside the bounds of Section 101, so that claims that have the practical effect of preempting natural phenomena are invalid. The Court also reaffirmed its decisions in *Benson*, *Flook*, and *Diamond* v. *Diehr*, 450 U.S. 175 (1981), and stated pointedly that it was not endorsing any prior Federal Circuit precedent. Moreover, the opinions by Justice Stevens (joined by Justices Ginsburg, Breyer, and Sotomayor) and Justice Breyer (joined in relevant part by Justice Scalia) each referenced *LabCorp* approvingly, and the majority opinion emphasized the need to set the Section 101 bar high enough to avoid flooding courts "with claims that would put a chill on creative endeavor and dynamic change." 130 S. Ct. at 3229. It was no surprise that, after *Bilski*, this Court granted certiorari in this case, vacated, and remanded.

D. The Federal Circuit's Second Decision Upholding The Patents.

On remand, the Federal Circuit refused to alter its decision, stating that this Court in *Bilski* "did not undermine" the Federal Circuit's prior analysis—an analysis that equated this Court's ultimate preemption standard with the Federal Circuit's "machine or transformation" test. App., *infra*, 14a. The Federal Circuit repeated its conclusion that alteration of a patient's body through metabolizing a drug, and the testing of the patient's blood for metabolite levels, were "transformations" that made the claims patentable. *Id.* at 15a-16a.

As for preemption, the Federal Circuit reasoned that "the claims do not preempt all uses of the natural correlations; they utilize them in a series of specific steps." *Id.* at 15a. But because the steps that lead up to the correlations are *not* uses of the correlations, they do nothing to narrow the scope of the patent and do not leave others free to use the correlations in different ways, including to develop new ways of treating patients. Instead, those data-gathering steps are simply the commonplace and well-understood steps of administering a drug and measuring its metabolites—the only way to assess the correlations. The result of the Federal Circuit's analysis is to uphold claims that in fact preempt anything that a physician might do with these naturally-existing correlations.

When confronted with *LabCorp*, the Federal Circuit again dismissed it, summarily stating that it "decline[d] to discuss a dissent"—even though the dissent analyzed and applied this Court's precedents, and Justice Breyer's opinion on the merits is the only word from any Justice on this critical issue. *Id.* at 16a n.2. No Justice disagreed with Justice Breyer's substantive analysis. The majority dismissed the petition in *LabCorp* solely because the issue had not been preserved or decided below.

REASONS FOR GRANTING THE PETITION

The Federal Circuit's decision conflicts with this Court's precedents because it broadly extends the "machine or transformation" test and fails to give effect to the "preemption" standard for patent-eligibility. Where a claim, like the Prometheus claims here, recites a natural phenomenon—and even the Federal Circuit agreed that the correlations in the Prometheus claims are natural phenomena—

but does not recite a real-world application of the phenomenon, and thus covers all such real-world applications, it is repugnant to the statute and invalid. Like the claims in *LabCorp*, the Prometheus claims do not come close to escaping the preemption prohibition.

I. THE FEDERAL CIRCUIT'S RULING RAISES THE SAME ISSUE THAT WARRANTED A GRANT OF CERTIORARI IN *LABCORP*.

A. This Court Previously Recognized The Exceptional Public Importance Of The Issue Presented.

Seven years ago, when the Court granted certiorari in *LabCorp*, it recognized the critical importance of the issue presented here to the United States economy and to the quality and cost of healthcare delivery. That a majority of Justices voted to dismiss the petition on procedural grounds does not undercut the issue's importance. The importance of the issue has only grown over the last seven years as a result of the Nation's efforts to constrain healthcare costs.

While the entire Court recognized the importance of the issue, the three Justices who would have decided the case on the merits highlighted the error in the Federal Circuit's approach. As set forth by Justice Breyer (joined by Justices Stevens and Souter), the claims there were directed to a method of "correlating" a blood homocysteine level with a deficiency in folate, just like the correlation between metabolites and patient condition in the Prometheus claims. Hence, "[t]here can be little doubt that the correlation [is] a 'natural phenomenon.'" 548 U.S. at 135. And the drafting of the claims to make the cor-

relation a "process" was plainly insufficient in *LabCorp*. The claim described a "natural law"—and dressing that law up "in the abstract patent language of a 'process'" was not enough to "avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge." *Id.* at 137. The blood testing steps of the claim were "nothing * * * that adds anything more of significance," leaving the "correlation [a]s an unpatentable 'natural phenomenon.'" *Id.* at 138. Accordingly, a simple patient blood test that leads to an unpatentable mental recognition is not a patentable process.

The Court's decision in *Bilski* provides strong support for this analysis. Although *Bilski* addressed a "business method" invention, all the Justices explicitly noted that scientific and biological laws must be available for anyone to copy and use in various ways.[4] The Court also warned the Federal Circuit that it was not free to return to its old legal standards. 130 S. Ct. at 3231 ("Nothing in today's opinion should be read as endorsing interpretations of § 101 that the Court of Appeals for the Federal Circuit has used in the past"). And five of the Justices quoted *LabCorp* with approval, and not just in passing. One opinion specifically endorsed *LabCorp*'s balancing analysis and catalogue of evils of over-broad patents, and another endorsed *LabCorp*'s discussion of the limits on patent-eligibility. *Bilski*, 130 S. Ct. at 3255,

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[4] *E.g.*, 130 S. Ct. at 3225 (Section 101 does not cover "laws of nature, physical phenomena, and abstract ideas") (majority); *id.* at 3235 (*Benson* and *Flook* stand for proposition that a patent may not claim a "phenomenon of nature or abstract idea") (Stevens, J., concurring); *id.* at 3258 ("phenomena of nature," "mental processes," and "abstract intellectual concepts are not patentable") (Breyer, J. concurring).

3259. It is not surprising that a majority of the Justices looked to Justice Breyer's *LabCorp* opinion: it provides a clear-cut summary of this Court's prior precedents in the life sciences context.

Despite this guidance, the Federal Circuit went in a completely different direction. It has twice in this case treated the *LabCorp* Justices' analysis in dismissive footnotes. And it has never explained how the facts of these two cases can be distinguished from one another. That would be impossible to do. The Federal Circuit's opinion shows that it would find the *LabCorp* claim to satisfy Section 101 because it involves taking a blood sample from a patient, assaying it, and then thinking about what the resulting natural correlation means for patient health.

This Court's guidance is now sorely needed. There is a broad consensus that appropriate application of Section 101 to biotechnology claims, and particularly the application of Section 101 to method claims involving natural, biological correlations, needs resolution. See, *e.g.*, Peter Lee, *Patent Law and the Two Cultures*, 120 YALE L.J. 2, 81 (2010) (observing after the GVR in this case that the Federal Circuit and this Court are "locked in dialogue" over the contours of process patentability, and questioning whether the Federal Circuit in this "important case" will "respond in kind" to this Court's approach in *Bilski* or continue with its "divergent cultur[e]"); Dan Vorhaus & John Conley, *Bilski and Biotech: Business as Usual, for Now*, GENOMICS L. REP. (June 28, 2010), available at www.genomicslawreport.com/index.php/2010/06/28/bilski-and-biotechnology ("Although the Court's narrow ruling left a direct treatment of the difficult issues surrounding biotechnology patents for another day, those issues continue to

loom large"); Margaret Kubick, *An Uncertain Future: The Impact of Medical Process and Diagnostic Method Patents on Healthcare in the United States*, 9 NW. J. OF TECH. & INTELLECTUAL PROP. 280, 292 (2010) ("To solve the current state of confusion surrounding process patent eligibility in the wake of *In re Bilski*, *Prometheus*, and *Bilski* v. *Kappos*," this Court "needs to provide a clear rule for patent applicants to follow").

Indeed, two related cases are now pending in the Federal Circuit, and there is no doubt they will be decided under erroneous law if this Court does not grant review.[5] There is nothing left to percolate, as the Federal Circuit is required by its own rules to follow the decision in this case. See *Hometown Fin., Inc.* v. *United States*, 409 F.3d 1360, 1365 (Fed. Cir. 2005); *South Corp.* v. *United States*, 690 F.2d 1368, 1370-1371 (Fed. Cir. 1982) (en banc). Beyond these known litigations are countless researchers and innovators who are paralyzed by patent monopolies like Prometheus's and by the Federal Circuit's ruling in this case. At the same time, countless patients are denied access to superior care at lower cost (to themselves, to insurers, and to state and federal governments).

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[5] *Ass'n for Molecular Pathology* v. *U.S. Patent & Trademark Office*, No. 2010-1406 ("*Myriad*"); *Classen Immunotherapies, Inc.* v. *Biogen Idec*, Nos. 2006-1634, 2006-1649. Notably, the Section 101 issue in this Petition stands alone and has been the subject of multiple rounds of briefing that have focused the arguments and produced definitive (and opposed) rulings from the courts below. The Federal Circuit has yet to decide either *Myriad* or—following a vacatur and remand by this Court in light of *Bilski*—*Classen*.

In short, this is not an issue that will benefit from the passage of more time. The Federal Circuit's lack of deference to *Bilski* on remand and adherence to rejected legal standards confirm the need for review by this Court.

B. This Court Has Long Invalidated Patent Claims That Attempt To Preempt All Uses Of Natural Phenomena.

The substantive analysis of Justices Breyer, Souter and Stevens in *LabCorp* is based on this Court's established precedent. Although Section 101 is expansive in its reach, *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980), it also is subject to important limits. In particular, a patent claim cannot preempt, either directly or by practical effect, a law of nature, natural phenomenon, or abstract scientific idea. As *Chakrabarty* observed:

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of * * * nature, free to all men and reserved exclusively to none.'

Id. at 309 (quoting *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). As the Court has also noted, "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Benson*, 409 U.S. at 67.

This exception to patentability applies not only to a patent claim that is aimed directly at a natural

phenomenon, but also to one whose "practical effect would be a patent on the [phenomenon] itself," because such a claim "wholly pre-empt[s]" all uses of the natural phenomenon. *Benson*, 409 U.S. at 71-72; see *Bilski*, 130 S. Ct. at 3230; *id* at 3253 (Stevens, J., concurring in the judgment); *id* at 3258 (Breyer, J., concurring in the judgment).

Thus, where a claim recites a law of nature or biological process, a court must look to whether the claim seeks protection for the phenomenon "in the abstract" or instead implements the phenomenon "in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect." *Diehr*, 450 U.S. at 191. The presence in a patent claim of a machine or transformation that uses a natural phenomenon may, in some cases, indicate that a patent claim encompasses *only* a definite subset of the uses for that phenomenon. But the role of machines and transformations in the analysis is subservient to the more general inquiry into preemption.

C. Prometheus's Claims Are Invalid Because They Preempt All Uses Of Natural Correlations.

The Prometheus claims, like the *LabCorp* claims, center on a natural phenomenon—the correlation between certain metabolite levels and patient health. That correlation is dictated by natural enzymatic activity inside the human body. Prometheus's own expert admitted that the drugs are "converted *naturally* by enzymes within the patient's body" into metabolites, as the district court found. The Federal Circuit did not disturb that finding by the district court, and agreed that the correlations were "naturally occurring." App., *infra*, 15a.

The Prometheus claims preempt all relevant uses of the correlations. In particular, the claims end with the step of recognizing the correlation and thus cover *anything* that a physician might do with her knowledge of the correlation. Prometheus's expert confirmed the sweeping preemptive effect of the claims by testifying that a physician who receives test results that identify the claimed ranges will infringe regardless of what she does with the information—it does not matter if she "crumples it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with." C.A. App. A13557-613558; see also C.A. Supp. App. A13805-13806. A clearer demonstration of the claims' extraordinary preemptive scope could not be imagined.

The preemptive impact of Prometheus's claims is particularly severe because they govern human thought that involves, in any medical context, metabolite ranges that Prometheus observed in patients who took gastrointestinal drugs. Dermatologist Dr. el-Azhary cannot stop thinking about Prometheus's ranges once she learns of them, even if her goal in reviewing a patient's test results is to find entirely different numbers relating only to dermatology. As a result, Prometheus has obtained an unwarranted monopoly across a broad field of medical practice. The preemptive scope of the Prometheus claims is unprecedented. It constitutes an embargo on research and analysis essential to the development of medical knowledge and patient care.

The way in which Prometheus's claims resemble those found invalid in *Benson* and *Flook*, and differ from those found valid in *Diehr*, confirm the proper result here. The claims in *Benson* recited a computa-

tion for converting numbers from one form to another, but did not recite what was to be done with the numbers once they were converted. Hence, the patent covered all such uses of the idea and would wholly preempt the underlying mathematical formula. 409 U.S. at 71-72. In a like manner, the claims in *Flook* recited a method for updating an alarm limit for use in a chemical process, but never recited what was to be done with the computation even though the claims did recite some "post-solution activity." 437 U.S. at 590. Because the claims covered all uses, they, like the claims in *Benson*, were held invalid.

By contrast, the claims in *Diehr*, which recited use of the Arrhenius equation, *also* recited a particular application of the equation: using the output of the equation to determine when to open or close an injection mold. In distinguishing that situation from *Benson* and *Flook*, the Court explained (450 U.S. at 187) that

> respondents here do not seek to patent a mathematical formula. Instead, they seek patent protection for a process of curing synthetic rubber. Their process admittedly employs a well-known mathematical equation, but they do not seek to pre-empt the use of that equation. Rather, they seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.

Prometheus's claims are like those in *Benson* and *Flook*, and unlike those in *Diehr*. In particular, claim 1 (quoted above) does not recite anything that should be done with a physician's recognition of a natural correlation, such as changing a patient dosage. The physician's thought process is analogous to the com-

puter processing in *Benson* and *Flook*—where the claims preempted all uses of the computer algorithms because those claims did not limit themselves to any real-world application of the algorithms. Thus, under this Court's well-established precedent, overreaching claims like those asserted by Prometheus are invalid.

D. The Federal Circuit's Broad Extension Of The "Machine Or Transformation" Test Has Produced A Square Conflict With This Court's Preemption Standard.

The Federal Circuit acknowledged that thinking about "possible dosage adjustments" is a "mental ste[p] and thus not patent-eligible *per se*." App., *infra*, 21a, 23a. Yet the court found the claims valid because they include two (and sometimes only one) "prior steps [that] provide useful information" (*id.* at 23a), even though those steps are well-known, are performed every day by countless medical personnel, and owe nothing at all to Prometheus. The court upheld the patents because those preparatory steps of administering the drug and determining a metabolite level involve "transformations" of matter (*id.* at 15a-20a)—transformations that, far from being any innovation, are simply the body's natural reaction to ingestion of drugs. Those bodily transformations in no way limit the uses that may be made of the admittedly natural correlations.

The Federal Circuit's elevation of these preparatory steps to case-dispositive importance rests on a two-fold misunderstanding. First, central to the court's preemption analysis was its observation that, rather than preempting all uses of the natural correlations, the claims "utilize them in a series of specific steps." App., *infra*, 15a. However, these steps are not

uses of the natural correlations, but just the opposite—natural actions that *lead up to* the natural correlations. Recitations in a claim involving machines or transformations are relevant when they show that the inventors have carved out a subset of real-world applications of a natural phenomenon, *e.g.*, by covering only particular uses of the phenomenon on a particular machine (and leaving open to the public other uses on other machines) or by applying the phenomenon in the real world by transforming something else (and leaving open to the public other transformations). That is precisely what happened in *Diehr*, where the patentee limited its claims to using the Arrhenius equation for a particular rubber molding process, and left open its use in other applications. 450 U.S. at 187-188. Prometheus, by contrast, has attempted to monopolize *all* uses of the natural, physician-recognized correlation.

Second, the Federal Circuit asserted that the preliminary steps were "specific treatment steps." In other words, the "inventive nature of the claimed methods stems * * * from the application of a natural phenomenon in a series of steps comprising particular methods of treatment." App., *infra*, 15a. But the preliminary steps are for testing, not treating. They are "nothing more than a data gathering step," which "cannot make an otherwise nonstatutory claim statutory." *In re Meyer*, 688 F.2d 789, 794 (CCPA 1982).

Prometheus's claims do not recite any amount of any drug to be given to any patient. They also say nothing about the ultimate use of the correlations, and thus cover all types of treatment, research, or any other kind of activity, as Prometheus's own expert confirmed. C.A. App. A13557-13558; see also C.A. Supp. App. A13805-13806. Patent drafters know

how to recite administration of "a therapeutically effective amount" of a drug for method of treatment claims. See, *e.g.*, *Geneva Pharms., Inc.* v. *GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-1384 (Fed. Cir. 2003) ("effective amount" is "a common and generally acceptable term" in claims covering pharmaceutical treatment methods); *Rapoport* v. *Dement*, 254 F.3d 1053, 1056 (Fed. Cir. 2001) (claim to treatment method "comprising administration of a therapeutically effective amount" of a drug). Prometheus was careful not to do so here.

These fundamental errors led the Federal Circuit to cobble together two well-known preliminary steps that were already part of the "storehouse of knowledge," and attach them to an admittedly insufficient mental step, to create a sprawling monopoly for Prometheus. The court's ruling, which rewards a mere drafter's trick, was erroneous, severely chills medical researchers like Dr. el-Azhary who are trying to make life-saving improvements in medical care, and should be reversed. See *Funk Bros.*, 333 U.S. at 130-132 ("packaging" "qualities [that] are the work of nature" with elements that make no difference in the way the natural principle operates is "not enough" for patentability); *LabCorp*, 548 U.S. at 137 ("one can reduce *any* process to a series of steps. The question is what those steps embody"); *Diehr*, 450 U.S. at 192 (refusing to "allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection").

The implications of the Federal Circuit's approach are truly astounding. Amici have pointed out, for example, that among the "huge swaths of basic medical knowledge" that "can be removed from

the public domain" by adopting drafting tricks like Prometheus's is "foundational knowledge" in the field of organ transplantation, where the dosage of anti-rejection drugs is critical and physicians make substantial effort to adjust treatment to ensure optimal therapeutic ranges for these drugs, using measurements of drug metabolites in patients' blood. Am. Br. of Quest Diagnostics, *et al.*, No. 09-490, at 8-10. A patent in that currently unpatented area, amici point out, would interfere with physicians' ability freely to adjust dosages to meet the needs of the particular patient. *Id.* at 10-11.

Non-medical uses of blood tests could likewise be constrained by over-expansive patents. Every state, for example, currently punishes driving with a blood alcohol level at or above 0.08 percent. See INSURANCE INSTITUTE FOR HIGHWAY SAFETY, DUI/DWI LAWS (March 2011), available at http://www.iihs.org/laws/dui.aspx. A patent claim that recites drawing blood, measuring blood alcohol content, and making a determination whether that level "indicates the need" to not drive a vehicle could under the Federal Circuit's analysis preclude states from considering changes to their DUI standards without paying the patent holder a license fee.

Of course, it makes no difference that Prometheus invested time and effort in researching this biological correlation, or that it believes its formula has practical value. $E=mc^2$ is not patentable (*Chakrabarty*, 447 U.S. at 309), even though the discovery has enormous value and was preceded by time-consuming data-gathering steps.

It was not the "intent of Congress" in Section 101 that "a process claim," still less one consisting solely of universally recognized data-gathering steps and a

natural phenomenon, should "confer power to block off whole areas of scientific development" by creating "a monopoly of knowledge." *Brenner* v. *Manson*, 383 U.S. 519, 534 (1966). Because such a patent "creates a monopoly of knowledge" that removes "incentive for others to undertake a search for uses," it "should be granted only if clearly commanded by the statute"—which here it is not. *Ibid.*

II. CERTIORARI SHOULD BE GRANTED TO AVOID OVER-BROAD PATENT MONOPOLIES THAT SUBVERT MEDICAL RESEARCH AND PATIENT TREATMENT.

This Court in *LabCorp* already found the issue presented here to be certworthy. This case is an appropriate vehicle to resolve the important issue left undecided there for lack of issue preservation. The Prometheus invention is easy to understand and centered on a plain natural phenomenon. The Section 101 issue was the only issue raised on appeal, and it was addressed directly and extensively by the Federal Circuit and the district court in opinions that reached opposite results. And because the Federal Circuit has exclusive jurisdiction over patent appeals from district courts (28 U.S.C. § 1295), erroneous decisions such as this one have immediate nationwide impact. Accordingly, this Court often grants review of Federal Circuit rulings based on the importance of the issue presented to the interpretation and application of the patent laws. *E.g., Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005). Review is especially warranted here because the Federal Circuit's analytical error is fundamental and will be repeated if not corrected by this Court.

The critical need for this Court to resolve that issue now is evidenced by the extensive amicus partic-

ipation in *LabCorp* and in this case, both at the Federal Circuit and previously on certiorari. Many *amici* stressed that patents like Prometheus's frustrate improvements in healthcare, drive up costs, and freeze innovation, as the dissenting Justices in *LabCorp* also recognized (548 U.S. at 138):

> [S]pecial public interest considerations reinforce my view that we should decide this case. To fail to do so threatens to leave the medical profession subject to the restrictions imposed by this individual patent and others of its kind. Those restrictions may inhibit doctors from using their best medical judgment; they may force doctors to spend unnecessary time and energy to enter into license agreements; they may divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations; they may raise the cost of health care while inhibiting its effective delivery.

AARP pointed out in its previous amicus brief in support of certiorari that "the increased rate at which the Patent Office has granted" patents on medical correlations "has led to severe restraint on the provision of medical care and a greatly increased cost and reduced availability of vital medical services, damaging the public health of the nation." Am. Br. of AARP, *et al.*, No. 09-490, at 4, 6, 13. These adverse consequences are profound given the sweep of the Federal Circuit's ruling, and extend far beyond gastrointestinal disorders. If Prometheus can obtain a patent on correlations between drug administration and resulting biological reactions in the human body, and prevent medical researchers and providers

from thinking about those correlations in different ways, a host of medical entrepreneurs will claim patent monopolies on blood tests with the same preclusive effects. A patent claimant could seek, for example, to monopolize the correlation between administration of anticoagulant drugs and chemical reactions in the blood, asserting that these reactions are "man-made" phenomena, and thereby preclude improvements in this commonplace and essential form of medical care. Unreasonably broad patent monopolies, which have no relationship to the contribution made to the art by the patent owners, will block all improvement in entire fields of medicine.

Therapeutic drug monitoring is fundamental to safely and effectively treating a variety of patient disorders. Mayo, and physicians throughout the world, routinely measure metabolite levels in patients being treated with an array of drugs, including those for the treatment of epilepsy, heart arrhythmias, and depression. See, *e.g.*, Buster Mannheimer, *et al.*, *Impact of Multiple Inhibitors or Substrates of Cytochrome P450 2D6 on Plasma Risperidone Levels in Patients on Polypharmacy*, 30 THERAPEUTIC DRUG MONITORING 565 (2008); Svein Johannessen, *et al.*, *Therapeutic Drug Monitoring of the Newer Antiepileptic Drugs*, 25 THERAPEUTIC DRUG MONITORING 347 (2003). Therapeutic monitoring is also important for medicines used in the treatment of organ transplant and cancer patients. See, *e.g.*, Teun van Gelder, *et al.*, *Therapeutic Drug Monitoring of Mycophenolate Mofetil in Transplantation*, 28 THERAPEUTIC DRUG MONITORING 145 (2006). Improvements in the administration of all these lifesaving drugs would be curtailed if patent claimants could assert a monopoly over every use of metabolite or other therapeutic correlations.

In this very case, Mayo sought to adjust the metabolite reference range deemed relevant by Prometheus to achieve more accurate results and improved patient care. App., *infra*, at 85a; Mayo Mem. in Support of Summary Judgment (Mar. 17, 2005), at 5-6 (Dkt. No. 15). But Prometheus blocked that innovation by asserting that it infringed Prometheus's exclusive right to specify relevant biological correlations. Prometheus thus claims the power to prevent all doctors—who considered metabolite levels on their own years before these patent claims were filed (see p. 5 n.2, *supra*)—from exercising independent medical judgment based on ordinary blood evaluations.

The harmful impact of overly broad intellectual property protection on innovation is also of more general concern for the U.S. economy. Academic commentary confirms that allowing patents to preempt important fields like medical diagnosis, by monopolizing scientific laws, would greatly increase costs and retard innovation. LAWRENCE LESSIG, THE FUTURE OF IDEAS 205-217 (2001) (describing negative impact of broad patent protection on innovation; "we should be most concerned when existing interests use the legal system to protect themselves against innovation"); WILLIAM LANDES & RICHARD POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 305-306 (2003) (patent monopolies on "scientific principles" threaten "enormous potential for rent seeking" and "enormous transaction costs that would be imposed on would-be users"); JAMES BESSEN & MICHAEL MEURER, PATENT FAILURE 8-9, 17, 27 (2008) (patents of "mental correlations" make it "very difficult to know [the patents'] boundaries," creating the "nee[d] to check a very large number of patents," inviting "disputes and litigation," and en-

couraging "patent trolls" to "opportunistically take advantage of poor patent notice to assert patents against unsuspecting firms"); DAN BURK & MARK LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT 123-124 (2009) (innovators must be able to work out new uses of abstractions and natural phenomena "without fear of patent liability" because patents "cove[r] entire concepts"); Robert Merges & Richard Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 915 (1990) ("[T]he real threat of a patent like this stems from the industry's close ties to science. * * * The Patent Office and courts should not permit the overprivatization of the scientific knowledge that makes the industry possible"); Lee Branstetter, *Do Stronger Patents Induce More Local Innovation?*, 7 J. INT'L ECON. L. 359, 369 (2004) ("well-structured research projects conducted by competent scholars" have "failed to find" innovation benefits from broad patent monopolies); Andrew Torrance & Bill Tomlinson, *Patents and the Regress of Useful Arts*, 10 COLUM. SCI. & TECH. L. REV. 130, 138, 162-167 (2009) (collecting economic research showing lack of stimulus to innovation from broad patent grants); see *Bilski*, 130 S. Ct. at 3253-3255 & nn.45-52 (Stevens, J, concurring in judgment).

At this time of paramount national concern over healthcare costs and quality, "a heavy burden of persuasion should be placed upon those who would extend such protection." Stephen Breyer, *The Uneasy Case for Copyright*, 84 HARV. L. REV. 281, 322-323 (1970) (citing research in patent and copyright fields). Prometheus has offered no such justification for its sweeping monopoly on medical thought and research.

Beyond this, the decision below cannot be reconciled with the ethical duties of physicians. As explained in the amicus brief filed in support of Mayo's prior petition by the American College of Medical Genetics and other medical organizations (at 9-11), and in the amicus brief of the American Medical Ass'n filed in *Bilski*, No. 08-964 (at 14), patent protection of Prometheus's claims conflicts with ethical standards that require physicians to spread knowledge—and improve diagnostic criteria—for the benefit of mankind.

The Federal Circuit's decision also poses exceptional threats to First Amendment freedoms. Throughout our Nation's history, the freedom to think—to consider what one has seen, to reach mental conclusions based on those observations, and to change one's future plans in light of those conclusions—has been deemed sacrosanct. Reflecting that tradition, this court held in *Ashcroft* v. *Free Speech Coalition*, 535 U.S. 234, 253 (2002), that speech is generally protected from government restriction because "[t]he right to think is the beginning of freedom, and speech must be protected from the government because speech is the beginning of thought." Federal legislation, like the patent laws, must be construed to avoid conflict with First Amendment freedoms whenever possible. See *Edward J. DeBartolo Corp.* v. *Florida Gulf Coast Bldg. & Constr. Trades Council*, 485 U.S. 568, 574-575 (1988); *New York* v. *Ferber*, 458 U.S. 747, 769 n.24 (1982); ACLU Am. Br. in *Bilski*, No. 2007-1130 (Fed. Cir. Apr. 3, 2008), at 5-7, 14, available at http://www.aclu.org/pdfs/freespeech/in_re_bilski_aclu_amicus.pdf (a patent like that at issue in *LabCorp* amounts "to a patent on pure thought or pure speech"; courts "should

interpret patent law doctrines * * * so as to avoid the difficult application of First Amendment doctrines").

The decision below would make mere thought actionable under patent law and threaten sanctions that include actual and treble damages. 35 U.S.C. § 284. Simply drawing a mental conclusion becomes, under the Federal Circuit's view, patent infringement, even without any further act. The infringement is complete when a doctor (like Dr. el-Azhary) has recognized a correlation between the patient's metabolite levels and the patient's status, regardless of what the doctor may do based on such recognition. This cannot be the legal rule in a Nation committed to the First Amendment and to the tradition of freedom of thought.

At bottom, the Federal Circuit's ruling authorizes patents monopolizing mere observation of natural phenomena that result from carrying out steps that are part of the public's storehouse of knowledge. That ruling flouts this Court's precedents and the fundamental purpose of the patent laws. And it puts a stranglehold on innovation and progress in the vital field of medical diagnosis.

CONCLUSION

The petition for a writ of certiorari should be granted to resolve the question left undecided in *LabCorp*.

Respectfully submitted.

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APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2008-1403

PROMETHEUS LABORATORIES, INC.,
Plaintiff-Appellant,

v.

MAYO COLLABORATIVE SERVICES (doing business as MAYO MEDICAL LABORATORIES) and MAYO CLINIC ROCHESTER,
Defendants-Appellees.

On Remand from the Supreme Court of the United States.

Decided: December 17, 2010.

Before RADER, *Chief Judge*, LOURIE and BRYSON, *Circuit Judges*.

LOURIE, *Circuit Judge*.

This case returns to this court on remand from the Supreme Court for further consideration in light of the Court's decision in *Bilski v. Kappos*,

561 U.S. --, 130 S. Ct. 3218 (2010). In *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 581 F.3d 1336 (Fed. Cir. 2009), we decided an appeal by Prometheus Laboratories, Inc. ("Prometheus") from a final judgment of the United States District Court for the Southern District of California granting summary judgment of invalidity of U.S. Patents 6,355,623 ("the '623 patent") and 6,680,302 ("the '302 patent") under 35 U.S.C. § 101. We held that the district court erred as a matter of law in finding Prometheus's asserted medical treatment claims to be drawn to non-statutory subject matter under this court's machine-or-transformation test, which we had held in *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008), to be the definitive test for determining the patentability of a process under § 101. Following our decision in this case, the Supreme Court held that the machine-or-transformation test, although "a useful and important clue," was not the sole test for determining the patent eligibility of process claims. *Bilski*, 130 S. Ct. at 3226-27. Based on that decision, the Court vacated and remanded our *Prometheus* decision. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 130 S. Ct. 3543 (2010) ("*GVR Order*"). On remand, we again hold that Prometheus's asserted method claims are drawn to statutory subject matter, and we again reverse the district court's grant of summary judgment of invalidity under § 101.

BACKGROUND

Prometheus is the sole and exclusive licensee of the '623 and '302 patents, which claim methods for determining the optimal dosage of thiopurine drugs used to treat gastrointestinal and non-gastrointestinal autoimmune diseases. These drugs

include 6-mercaptopurine ("6-MP") and azathioprine ("AZA"), a pro-drug that upon administration to a patient converts to 6-MP, both of which are used to treat inflammatory bowel diseases ("IBD") such as Crohn's disease and ulcerative colitis. 6-MP is broken down by the body into various 6-MP metabolites, including 6-methylmercaptopurine ("6-MMP") and 6-thioguanine ("6-TG") and their nucleotides.[1]

Although drugs such as 6-MP and AZA have been used for years to treat autoimmune diseases, non-responsiveness and drug toxicity may complicate treatment in some patients. Accordingly, the patents claim methods that seek to optimize therapeutic efficacy while minimizing toxic side effects. As written, the claimed methods typically include two separately lettered steps: (a) "administering" a drug that provides 6-TG to a subject, and (b) "determining" the levels of the drug's metabolites, 6-TG and/or 6-MMP, in the subject. *See, e.g.*, '623 patent claim 1. The measured metabolite levels are then compared to pre-determined metabolite levels, "wherein" the measured metabolite levels "indicate a need" to increase or decrease the level of drug to be administered so as to minimize toxicity and maximize treatment efficacy. *See, e.g., id.* In particular, according to the patents, a 6-TG level greater than about 400 picomole ("pmol") per 800 million red blood cells or a 6-MMP level greater than about 7,000 pmol per 800 million red blood cells indicates that a downward adjustment in drug dosage may be required to avoid toxic side effects. *See id.* col.20 ll.22, 54. Conversely,

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[1] For the purposes of this opinion, "6-TG" encompasses 6-thioguanine nucleotides.

according to the patents, a 6-TG level of less than about 230 pmol per 800 million red blood cells indicates a need to increase the dosage to ensure therapeutic efficacy. *See id.* col.20 ll.18-19.

Claim 1 of the '623 patent is representative of the independent claims asserted by Prometheus in this case:

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) *administering* a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) *determining* the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells *indicates a need* to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

'623 patent claim 1 (emphases added). Claim 1 of the '302 patent is substantially the same, with the addition of determining 6-MMP levels in addition to 6-TG levels. Claim 46 of the '623 patent dispenses with the

"administering" step and claims only the "determining" step:

> 46. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) *determining* the level of 6-thioguanine or 6-thylmercaptopurine in a subject administered a drug selected from the group consisting of 6-mercaptopurine, azathiop[u]rine, 6-thioguanine, and 6-methylmercaptoriboside, said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells *indicates a need* to increase the[] amount of said drug subsequently administered to said subject, and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells or a level of 6-methylmercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

'623 patent claim 46 (emphases added).

Prometheus marketed a PROMETHEUS Thiopurine Metabolites test (formerly known as the PRO-PredictRx® Metabolites test) that used the technology covered by the patents in suit. Mayo Collaborative Services and Mayo Clinic Rochester (collectively,

"Mayo") formerly purchased and used Prometheus's test, but in 2004, Mayo announced that it intended to begin using internally at its clinics and selling to other hospitals its own test. Mayo's test measured the same metabolites as Prometheus's test, but Mayo's test used different levels to determine toxicity of 6-TG and 6-MMP.

On June 15, 2004, Prometheus sued Mayo for infringement of the '623 and '302 patents. Prometheus asserted independent claims 1, 7, 22, 25, and 46 of the '623 patent and independent claim 1 of the '302 patent. Prometheus also asserted several dependent claims that require either that the measurement of the metabolites be performed using high pressure liquid chromatography, *see* '623 patent claims 6, 14, 24, 30, and 53, or that the thiopurine drug used be one of four specified drugs, *see id.* claims 32, 33, 35, and 36. Mayo rescinded its announcement shortly after Prometheus filed suit, and has yet to launch its test.

On November 22, 2005, the district court held on cross-motions for summary judgment that Mayo's test literally infringed claim 7 of the '623 patent. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200, slip op. at 23 (S.D. Cal. Nov. 22, 2005) (Dkt. No. 227). In its opinion, the court construed "indicates a need" to mean "a warning that an adjustment in dosage may be required." *Id.* at 18. This construction did not require doctors to adjust drug dosage if the metabolite level reached the specified levels; rather, the court found the two "wherein" phrases to mean "that when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required, if

the doctor believes that is the proper procedure." *Id.* at 17-18.

On January 29, 2007, Mayo filed a motion for summary judgment of invalidity, arguing that the patents in suit are invalid because they claim subject matter unpatentable under 35 U.S.C. § 101. Specifically, Mayo contended that the patents impermissibly claim natural phenomena—the correlations between, on the one hand, thiopurine drug metabolite levels and, on the other hand, efficacy and toxicity—and that the claims wholly preempt use of the natural phenomena.

On March 28, 2008, the district court granted Mayo's motion for summary judgment of invalidity under § 101. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200, 2008 WL 878910 (S.D. Cal. Mar. 28, 2008) ("*Invalidity Opinion*"). First, the court found that the patents only claimed the correlations between certain thiopurine drug metabolite levels and therapeutic efficacy and toxicity. The court reasoned that, as construed in the November 2005 summary judgment order, the claims have three steps: (1) administering the drug to a subject, (2) determining metabolite levels, and (3) being warned that an adjustment in dosage may be required. The court stated that the fact that the inventors framed the claims as treatment methods does not render the claims patent-eligible subject matter. Rather, the court found that the "'administering' and 'determining' steps are merely necessary data-gathering steps for any use of the correlations" and that "as construed, the final step—the 'warning' step (*i.e.*, the 'wherein' clause)—is only a mental step." The court noted that the warning step does not re-

quire any actual change in dosage and that "it is the metabolite levels themselves that 'warn' the doctor that an adjustment in dosage may be required." *Id.* With this understanding of the claims, the court concluded that the claims recited the correlations between particular concentrations of 6-TG and 6-MMP and therapeutic efficacy or toxicity in patients taking AZA drugs. *Id.* at *6.

Second, the district court found that those correlations were natural phenomena, not patent-eligible inventions because the correlations resulted from a natural body process. The court stated that the inventors did not "invent" the claimed correlation; rather, "6-TG and 6-MMP are products of the natural metabolizing of thiopurine drugs, and the inventors merely observed the relationship between these naturally produced metabolites and therapeutic efficacy and toxicity." *Id.* at *7. Finally, the court determined that "[b]ecause the claims cover the correlations themselves, it follows that the claims 'wholly preempt' the correlations." *Id.* at *11. Thus, the court concluded that there was no genuine issue of material fact to be resolved as to whether the patents in suit were directed to statutory subject matter and found by clear and convincing evidence that the claims were invalid under § 101. *Id.* at *14. On May 16, 2008, the district court entered final judgment, and Prometheus timely appealed.

On appeal, we reversed and upheld the asserted claims' validity under what was at the time this court's "definitive test" for determining whether a process is patentable subject matter under § 101: the machine-or-transformation test. *Prometheus,* 581 F.3d at 1342. Under the machine-or-transformation

test, a claimed process is patent eligible if it (1) is tied to a particular machine or apparatus, or (2) transforms a particular article into a different state or thing. *Id.* (quoting *Bilski*, 545 F.3d at 954). We held that both the "administering" and "determining" steps were transformative and not merely data-gathering steps under the second prong of the test, and as such the claims did not wholly preempt the use of the recited correlations between metabolite levels and drug efficacy or toxicity. *Id.* at 1345-49.

Following our decision in *Prometheus*, the Supreme Court issued a decision rejecting the machine-or-transformation test as the sole, definitive test for determining the patent eligibility of a process under § 101. *Bilski*, 130 S. Ct. at 3226-27. Instead, the Court declined to adopt any categorical rules outside the well-established exceptions for laws of nature, physical phenomena, and abstract ideas, and resolved the case based on its decisions in *Gottschalk v. Benson*, 409 U.S. 63 (1972), *Parker v. Flook*, 437 U.S. 584 (1978), and *Diamond v. Diehr*, 450 U.S. 175 (1981), holding that *Bilski's* claims to methods of hedging risk are not patentable processes because they attempt to patent abstract ideas. *Id.* at 3226, 3229-30. The Court did not, however, reject the machine-or-transformation test, but rather characterized the test as "a useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101." *Id.* at 3227.

The Court then granted Mayo's petition for certiorari, vacated our decision holding Prometheus's method of treatment claims to cover patent-eligible subject matter under the machine-or-transformation

test, and remanded the case for consideration in light of the Court's *Bilski* decision. On September 1, 2010, we requested that the parties simultaneously submit briefs, without further oral argument, to address the effect of the Supreme Court's decision in *Bilski* on the disposition of this case. In view of this additional briefing and the Supreme Court's guidance in *Bilski*, we again hold that Prometheus's method claims recite patentable subject matter under § 101.

DISCUSSION

We review the district court's grant of summary judgment *de novo*. *AT&T Corp. v. Excel Commc'ns*, 172 F.3d 1352, 1355 (Fed. Cir. 1999). Summary judgment is appropriate if there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c). Whether a patent claim is directed to statutory subject matter is a question of law that we review *de novo*. *AT&T*, 172 F.3d at 1355.

I.

The issue again before us is whether Prometheus's method claims meet the requirements of § 101. The text of the statute provides that:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent thereof, subject to the conditions and requirements of this title.

35 U.S.C. § 101. The Supreme Court has consistently construed § 101 broadly. Most recently, in *Bilski*, the Court stated that by choosing expansive terms to

specify four independent patent-eligible categories of inventions or discoveries—processes, machines, manufactures, and compositions of matter—and by modifying those terms with the comprehensive "any," Congress plainly contemplated that § 101 would be given wide scope. 130 S. Ct. at 3225 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). "Congress took this permissive approach to patent eligibility to ensure that 'ingenuity should receive a liberal encouragement.'" *Id.* (quoting 5 *Writings of Thomas Jefferson* 75-76 (H. Washington ed. 1871)).

Yet, it is equally well-established that § 101, while broad, is not unlimited. "The Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.' " *Id.* (quoting *Chakrabarty*, 447 U.S. at 309). Although not compelled by the statutory text, the Court has held that "these exceptions have defined the reach of the statute as a matter of statutory *stare decisis* going back 150 years," *id.* (citing *Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 174-75 (1853)), and "[t]he concepts covered by these exceptions are 'part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none,'" *id.* (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)); *see also Benson*, 409 U.S. at 67 ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.").

The Supreme Court has also established that while a law of nature, natural phenomenon, or abstract idea cannot be patented, "an *application* of a

law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 188). In making this determination, the Court has made clear that a claim must be considered as a whole; it is "inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Id.* (quoting *Diehr*, 450 U.S. at 188). Nonetheless, a scientific principle cannot be made patentable by limiting its use to a particular technological environment or by adding insignificant post-solution activity. *Diehr*, 450 U.S. at 191-92.

In light of the Supreme Court's decision in *Bilski*, patent eligibility in this case turns on whether Prometheus's asserted claims are drawn to a natural phenomenon, the patenting of which would entirely preempt its use as in *Benson* or *Flook*, or whether the claims are drawn only to a particular application of that phenomenon as in *Diehr*. *Bilski*, 130 S.Ct. at 3230. We conclude they are drawn to the latter.

II.

We turn to the parties' arguments on remand. Prometheus argues that neither the Supreme Court's *Bilski* decision nor the Court's *GVR Order* compels a different outcome on remand, and therefore we should again reverse the district court's judgment of invalidity under § 101. Regarding *Bilski*, Prometheus contends that the Court held only that patents that do *not* satisfy the machine-or-transformation test are not necessarily *un*patentable and did not overrule the long-established view that claims that satisfy the machine-or-transformation test, like Prometheus's, necessarily satisfy § 101. But regardless, Prometheus

argues, its asserted claims not only satisfy the machine-or-transformation test, but also are not drawn to mere abstractions. Specifically, Prometheus argues that its asserted claims involve a particular transformation of a patient's body and bodily sample and use particular machines to determine metabolite concentrations in a bodily sample (*e.g.*, via high pressure liquid chromatography), thus satisfying either prong of the machine-or-transformation test. Prometheus further argues that its claims also involve an application of a law of nature, not the law itself, because they recite specific means of treating specific diseases using specific drugs, and therefore do not preempt the abstract idea of calibrating drug dosages to treat disease.

Mayo argues that the Supreme Court in *Bilski* reaffirmed that preemption is the controlling standard for § 101 under the Court's *Benson*, *Flook*, and *Diehr* precedents and made clear that while a machine-or-transformation test may inform the analysis, that test is not outcome determinative. And, according to Mayo, under the governing preemption standard, Prometheus's claims are invalid because they preempt all practical use of naturally occurring correlations between metabolite levels and drug efficacy and any machine or transformation present in the claims is merely insignificant post-solution activity. Mayo also asserts that the carefully considered opinion of three Justices—allegedly cited approvingly by five Justices in *Bilski*—rejected Prometheus's machine-or-transformation argument for nearly identical claims in *Laboratory Corp. of America Holdings, Inc. v. Metabolite Laboratories, Inc.*, 548 U.S. 124, 138-39 (2006), concluding that the claims do not cover a process for transforming a bodily sample, but ra-

ther merely instruct the user to obtain test results and think about them. Finally, Mayo claims that the Supreme Court's decision to GVR our earlier decision in this case indicates that a different analysis is required of us on remand.

We disagree with Mayo. We do not think that either the Supreme Court's *GVR Order* or the Court's *Bilski* decision dictates a wholly different analysis or a different result on remand. In our pre-*Bilski* decision in this case, we held not only that Prometheus's asserted claims recite transformative "administering" and "determining" steps, but also that Prometheus's claims are drawn not to a law of nature, but to a particular application of naturally occurring correlations, and accordingly do not preempt all uses of the recited correlations between metabolite levels and drug efficacy or toxicity. The Supreme Court's decision in *Bilski* did not undermine our preemption analysis of Prometheus's claims and it rejected the machine-or-transformation test only as a definitive test. The Court merely stated that "[t]he Court of Appeals incorrectly concluded that this Court has endorsed the machine-or-transformation test *as the exclusive test*." 130 S. Ct. at 3226 (emphasis added). The Court stated that it had previously noted in *Benson*, 409 U.S. at 70, that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Id.* at 3227. Thus, the Court did not disavow the machine-or-transformation test. And, as applied to the present claims, the "useful and important clue, an investigative tool," leads to a clear and compelling conclusion, *viz.*, that the present claims pass muster under

§ 101. They do not encompass laws of nature or preempt natural correlations.

III.

As before, we again hold that Prometheus's asserted method claims recite a patent-eligible application of naturally occurring correlations between metabolite levels and efficacy or toxicity, and thus do not wholly preempt all uses of the recited correlations. As discussed below, the claims recite specific treatment steps, not just the correlations themselves. And the steps involve a particular application of the natural correlations: the treatment of a specific disease by administering specific drugs and measuring specific metabolites. As such, and contrary to Mayo's assertions, the claims do not preempt all uses of the natural correlations; they utilize them in a series of specific steps. *See Diehr*, 450 U.S. at 187 ("Their process admittedly employs a well-known mathematical equation, but they do not seek to preempt the use of that equation. Rather, they seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process."). The inventive nature of the claimed methods stems not from preemption of all use of these natural processes, but from the application of a natural phenomenon in a series of steps comprising particular methods of treatment. Other drugs might be administered to optimize the therapeutic efficacy of the claimed treatment.

We similarly reaffirm that the treatment methods claimed in Prometheus's patents in suit satisfy the transformation prong of the machine-or-transformation test, as they "transform an article into a different state or thing," and this transformation

is "central to the purpose of the claimed process." *See Bilski*, 545 F.3d at 962. The transformation is of the human body and of its components following the administration of a specific class of drugs and the various chemical and physical changes of the drugs' metabolites that enable their concentrations to be determined. We thus have no need to separately determine whether the claims also satisfy the machine prong of the test.

Contrary to the district court and Mayo's arguments on remand, we do not view the disputed claims as merely claiming natural correlations and data-gathering steps.[2] The asserted claims are in effect claims to methods of treatment, which are always transformative when one of a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition. More specifically, Prometheus here claimed methods for optimizing ef-

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[2] Mayo, as did the district court, points to the opinion of three Justices dissenting from the dismissal of the grant of certiorari in *Lab. Corp.*, 548 U.S. 124, (Breyer, J., dissenting from dismissal of certiorari as improvidently granted). *See Invalidity Opinion*, 2008 WL 878910, at *8 (discussing the dissent in *Lab. Corp.* at length and finding Justice Breyer's reasoning persuasive). Again, with respect, we decline to discuss a dissent; it is not controlling law, and it involved different claims from the ones at issue here. Mayo further claims that five Justices in two concurrences cited *Lab. Corp.* with approval in *Bilski*, but such citations fail to transform a dissent into controlling law. Moreover, one concurrence cites *Lab. Corp.* for the proposition that "*too much* patent protection can impede rather than 'promote the Progress of . . . useful Arts,' " in arguing for a categorical rule that business method patents do not qualify as patent-eligible processes under § 101. *Bilski*, 130 S. Ct. at 3255 (Stevens, J., concurring). But this case does not involve business method patents.

ficacy and reducing toxicity of treatment regimes for gastrointestinal and non-gastrointestinal autoimmune diseases that utilize drugs providing 6-TG by administering a drug to a subject. The invention's purpose to treat the human body is made clear in the specification and the preambles of the asserted claims. *See* '623 patent col.2 ll.16-19 ("The present invention provides a method of optimizing therapeutic efficacy of 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder."); *see, e.g., id.* claim 1 ("A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising . . ."); *id.* claim 7 ("A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising . . ."); *id.* claim 22 ("A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease, comprising . . .").

When administering a drug such as AZA or 6-MP, the human body necessarily undergoes a transformation. The drugs do not pass through the body untouched without affecting it. In fact, the transformation that occurs, *viz.*, the effect on the body after metabolizing the artificially administered drugs, is the entire purpose of administering these drugs: the drugs are administered to provide 6-TG, which is thought to be the drugs' active metabolite in the treatment of disease, to a subject. *See* '623 patent col.1 ll.49-51. The fact that the change of the administered drug into its metabolites relies on natural processes does not disqualify the administering step from the realm of patentability. As Prometheus points out, quite literally every transformation of physical matter can be described as occurring according to natural processes and natural law. Transfor-

mations operate by natural principles. The transformation here, however, is the result of the physical administration of a drug to a subject to transform—*i.e.*, treat—the subject, which is itself not a natural process. "It is virtually self-evident that a process for a chemical or physical transformation of *physical objects or substances* is patent-eligible subject matter." *Bilski*, 545 F.3d at 962. The administering step, therefore, is not merely data-gathering but a significant transformative element of Prometheus's claimed methods of treatment that is "sufficiently definite to confine the patent monopoly within rather definite bounds." *Benson*, 409 U.S. at 70.

Not all of the asserted claims, however, contain the administering step. That omission, which occurs in claims 46 and 53 of the '623 patent, does not diminish the patentability of the claimed methods because we also hold that the determining step, which is present in each of the asserted claims, is transformative and central to the claimed methods. Determining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation. Some form of manipulation, such as the high pressure liquid chromatography method specified in several of the asserted dependent claims or some other modification of the substances to be measured, is necessary to extract the metabolites from a bodily sample and determine their concentration. As stated by Prometheus's expert, "at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue." Decl. of Dr. Yves Théorêt ¶ 6, *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200 (S.D. Cal. Mar. 29, 2007) (Dkt. No. 528-3). That is clearly a transformation. In fact, Mayo does not dispute that determining

metabolite levels in the clinical samples taken from patients is transformative, but argues that this transformation is merely a necessary data-gathering step for use of the correlations. On the contrary, this transformation is central to the purpose of the claims, since the determining step is, like the administering step, a significant part of the claimed method. Measuring the levels of 6-TG and 6-MMP is what enables possible adjustments to thiopurine drug dosage to be detected for optimizing efficacy or reducing toxicity during a course of treatment. The determining step, by working a chemical and physical transformation on physical substances, likewise sufficiently confines the patent monopoly, as required by the machine-or-transformation test.

A further requirement for patent-eligibility is ensuring that the involvement of the transformation in Prometheus's claimed process is "not merely insignificant extra-solution activity." *Flook*, 437 U.S. at 590. As made clear from the discussion above, the administering and determining steps are transformative and are central to the claims rather than merely insignificant extra-solution activity.

The crucial error the district court made in reaching the opposite conclusion was failing to recognize that the first two steps of the asserted claims are not merely data-gathering steps. *See Invalidity Opinion*, 2008 WL 878910, at *6 (finding that "the 'administering' and 'determining' steps are merely necessary data-gathering steps for any use of the correlations"). While it is true that the administering and determining steps gather useful data, it is also clear that the presence of those two steps in the claimed processes is not "merely" for the purpose of gathering data. In-

stead, the administering and determining steps are part of a treatment protocol, and they are transformative. As explained above, the administering step provides thiopurine drugs for the purpose of treating disease, and the determining step measures the drugs' metabolite levels for the purpose of assessing the drugs' dosage during the course of treatment.

Given the integral involvement of the administering and determining steps in Prometheus's therapeutic methods, this case is easily distinguishable from prior cases that found asserted method claims to be unpatentable for claiming data-gathering steps and a fundamental principle. Perhaps the case that offers the closest comparison is *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989), but the asserted claims found unpatentable in that case are readily distinguished from those in the instant action. In *Grams*, the applicant claimed a process that involved (1) performing a clinical test on individuals and (2) based on the data from that test, determining if an abnormality existed and determining possible causes of any abnormality by using an algorithm. We found that this process was not drawn to patentable subject matter because the essence of the claimed process was the mathematical algorithm, rather than any transformation of the tested individuals. 888 F.2d at 839-41. More specifically, the *Grams* process was unpatentable because "it was merely an algorithm combined with a data-gathering step," *i.e.*, performing a clinical test. *Bilski*, 545 F.3d at 963. The claims did not require the performing of clinical tests on individuals that were transformative—and thus rendering the entire process patentable subject matter—because the tests were just to "obtain data." *Grams*, 888 F.2d at 840. The patent and thus the court focused only on the al-

gorithm rather than the clinical tests purported to be covered by the claims.

Here, unlike the clinical test recited in *Grams*, the administering and determining steps in Prometheus's claimed methods are not "merely" data-gathering steps or "insignificant extra-solution activity"; they are part of treatment regimes for various diseases using thiopurine drugs. *See Bilski*, 545 F.3d at 963 (discussing *Grams*). As a result, the administering and determining steps are not insignificant extra-solution activity, and the claims are therefore not drawn merely to correlations between metabolite levels and toxicity or efficacy.

We agree with the district court that the final "wherein" clauses are mental steps and thus not patent-eligible per se. However, although they alone are not patent-eligible, the claims are not simply to the mental steps. A subsequent mental step does not, by itself, negate the transformative nature of prior steps. Thus, when viewed in the proper context, the final step of providing a warning based on the results of the prior steps does not detract from the patentability of Prometheus's claimed methods as a whole. The data that the administering and determining steps provide for use in the mental steps are obtained by steps well within the realm of patentable subject matter; the addition of the mental steps to the claimed methods thus does not remove the prior two steps from that realm. No claim in the Prometheus patents claims only mental steps. Therefore, contrary to Mayo's assertions, a physician who only evaluates the result of the claimed methods, without carrying out the administering and/or determining

steps that are present in all the claims, cannot infringe any claim that requires such steps.

This analysis is consistent with *In re Abele*, 684 F.2d 902 (CCPA 1982). In *Abele*, a method claim called for the use of X-ray attenuation data, which necessarily involved production, detection, and display with a CAT scan. The method also called for use of an algorithm. We found that the claim was patentable because removal of the algorithm still left all the steps of a CAT scan in the claim; thus, the production and detection could not be considered "mere antecedent steps to obtain values for solving the algorithm. . . . We view the production, detection, and display steps as manifestly statutory subject matter, and are not swayed from this conclusion by the presence of an algorithm in the claimed method." *Id.* at 908. In the instant case, the presence of mental steps similarly does not detract from the patentability of the administering and determining steps.

As we explained in *Bilski*,

> [I]t is inappropriate to determine the patent eligibility of a claim as a whole based on whether selected limitations constitute patent-eligible subject matter. After all, even though a fundamental principle itself is not patent-eligible, processes incorporating a fundamental principle may be patent-eligible. Thus, it is irrelevant that any individual step or limitation of such processes by itself would be unpatentable under § 101.

545 F.3d at 958 (citations omitted). Such is the case here. Although the wherein clauses describe the mental processes used to determine the need to

change the dosage levels of the drugs, each asserted claim as a whole is drawn to patentable subject matter. Although a physician is not required to make any upward or downward adjustment in dosage during the "warning" step, the prior steps provide useful information for possible dosage adjustments to the method of treatment using thiopurine drugs for a particular subject. Viewing the treatment methods as a whole, Prometheus has claimed therapeutic methods that determine the optimal dosage level for a course of treatment. In other words, when asked the critical question, "What did the applicant invent?," *Grams*, 888 F.2d at 839 (citation omitted), the answer is a series of transformative steps that optimizes efficacy and reduces toxicity of a method of treatment for particular diseases using particular drugs.

In light of the foregoing analysis, we hold that Prometheus's asserted method claims satisfy the preemption test as well as the transformation prong of the machine-or-transformation test.

CONCLUSION

For the foregoing reasons, we reverse the judgment of the district court and remand to the court with instructions to deny Mayo's motion for summary judgment that the asserted claims are invalid under § 101.

REVERSED and REMANDED

APPENDIX B

SUPREME COURT OF THE UNITED STATES

09-490

MAYO COLLABORATIVE SERVICES,
dba Mayo Medical Laboratories, et al., Petitioners,

v.

PROMETHEUS LABORATORIES, INC.

June 29, 2010.

Case below, 581 F.3d 1336.

On petition for writ of certiorari to the United States Court of Appeals for the Federal Circuit. The petition for a writ of certiorari is granted. The judgment is vacated, and the case is remanded to the United States Court of Appeals for the Federal Circuit for further consideration in light of *Bilski* v. *Kappos*, 561 U.S. ---- (2010).

APPENDIX C

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

2008-1403

PROMETHEUS LABORATORIES, INC.,
Plaintiff-Appellant,
v.
MAYO COLLABORATIVE SERVICES (doing business as Mayo Medical Laboratories) and MAYO CLINIC ROCHESTER,
Defendants-Appellees.

Appeal from the United States District Court for the Southern District of California in Case No. 04-CV-1200, Judge John A. Houston.

Decided: September 16, 2009

Before MICHEL, *Chief Judge*, LOURIE, *Circuit Judge*, and CLARK, District Judge.*
LOURIE, *Circuit Judge*.

Prometheus Laboratories, Inc. ("Prometheus") appeals from the final judgment of the United States District Court for the Southern District of California granting summary judgment of invalidity of U.S. Pa-

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* Honorable Ron Clark, District Judge, United States District Court for the Eastern District of Texas, sitting by designation.

tents 6,355,623 ("the '623 patent") and 6,680,302 ("the '302 patent") under 35 U.S.C. § 101. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200, 2008 WL 878910 (S.D. Cal. Mar. 28, 2008) ("*Invalidity Opinion*"). Because the district court erred as a matter of law in finding the asserted claims to be drawn to non-statutory subject matter, we reverse.

I. BACKGROUND

Prometheus is the sole and exclusive licensee of the '623 patent and the '302 patent. The patents claim methods for calibrating the proper dosage of thiopurine drugs, which are used for treating both gastrointestinal and non-gastrointestinal autoimmune diseases. These drugs include 6-mercaptopurine ("6-MP") and azathiopurine ("AZA"), a pro-drug that upon administration to a patient converts to 6-MP, which are used to treat inflammatory bowel diseases ("IBD") such as Crohn's disease and ulcerative colitis. 6-MP is broken down by the body into various 6-MP metabolites, including 6-methyl-mercaptopurine ("6-MMP") and 6-thioguanine ("6-TG") and their nucleotides.[1] The patents involve measurements of these two metabolites. Drugs that deliver 6-TG are widely used for their cytotoxic and immunosuppressive properties.

Although drugs such as 6-MP and AZA have been used for years to treat autoimmune diseases, non-responsiveness and drug toxicity may complicate treatment in some patients. To that end, the patents claim methods that seek to optimize therapeutic effi-

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[1] For the purposes of this opinion, "6-TG" encompasses 6-thioguanine nucleotides.

cacy while minimizing toxic side effects. As written, the methods typically include two separately lettered steps: (a) "administering" a drug that provides 6-TG to a subject and (b) "determining" the levels of the drug's metabolites, 6-TG and/or 6-MMP, in the subject. *See, e.g.*, '623 patent claim 1. The measured metabolite levels are then compared to pre-determined metabolite levels, "wherein" the measured metabolite levels "indicate a need" to increase or decrease the level of drug to be administered so as to minimize toxicity and maximize efficacy of treatment. *See, e.g.*, *id.* In particular, according to the patents, a 6-TG level greater than about 400 picomole ("pmol") per 800 million red blood cells or a 6-MMP level greater than about 7000 pmol per 800 million red blood cells indicates that a downward adjustment in drug dosage may be required in order to avoid toxic side effects. *See id.* col.20 ll.22, 54. Conversely, according to the patents, a 6-TG level of less than about 230 pmol per 800 million red blood cells indicates a need to increase the dosage to ensure therapeutic efficacy. *See id.* col.20 ll.18-19.

Claim 1 of the '623 patent is representative of the independent claims asserted by Prometheus in this case:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject hav-

> ing said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than
>
> about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than
>
> about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Claim 1 of the '302 patent is substantially the same, with the inclusion of determining 6-MMP levels in addition to 6-TG.

Prometheus marketed a PROMETHEUS Thiopurine Metabolites test (formerly known as the PRO-PredictRx® Metabolites test) that used the technology covered by the patents in suit. Mayo Collaborative Services and Mayo Clinic Rochester (together, "Mayo") formerly purchased and used Prometheus's test, but in 2004, Mayo announced that it intended to begin using internally at its clinics and selling to other hospitals its own test. Mayo's test measured the same metabolites as Prometheus's test, but Mayo's test used different levels to determine toxicity of 6-TG and 6-MMP.

On June 15, 2004, Prometheus sued Mayo for infringement of the patents. Prometheus asserted independent claims 1, 7, 22, 25, and 46 of the '623 patent and independent claim 1 of the '302 patent. Most of these claims cover a "method for optimizing

therapeutic efficacy" and/or "reducing toxicity" in patients taking a drug such as AZA or 6-MP in the treatment of an immune-mediated gastrointestinal disease. *See* '623 patent claims 1, 7, 25, & 46; '302 patent claim 1. One independent claim was for treatment of a non-IBD autoimmune disease. *See* '623 patent claim 22. Prometheus also asserted several dependent claims that require either that the measurement of the metabolites is done using high pressure liquid chromatography, *see* '623 patent claims 6, 14, 24, 30, and 53, or that the thiopurine drug used is one of four specified drugs, *see* '623 patent claims 32, 33, 35, and 36. Mayo rescinded its announcement shortly after the lawsuit was filed and still has not launched its test.

On November 22, 2005, the district court held on cross-motions for summary judgment that Mayo's test literally infringed claim 7 of the '623 patent. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200, slip op. at 23 (S.D. Cal. Nov. 22, 2005) (Dkt. No. 227). In its opinion, the court construed "indicates a need" to mean "a warning that an adjustment in dosage may be required." *Id.* at 18. This construction did not require doctors to adjust drug dosage if the metabolite level reached the specified levels; rather, the court found the wherein phrases to mean "that when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required, if the doctor believes that is the proper procedure." *Id.* at 17-18.

On January 29, 2007, Mayo filed a motion for summary judgment of invalidity, arguing that the patents in suit are invalid because they claim unpatentable subject matter under 35 U.S.C. § 101. Spe-

cifically, Mayo contended that the patents impermissibly claim natural phenomena—the correlations between, on the one hand, thiopurine drug metabolite levels and, on the other hand, efficacy and toxicity—and that the claims wholly preempt use of the natural phenomena.

On March 28, 2008, the district court granted Mayo's motion for summary judgment of invalidity under § 101. First, the court found that the patents claimed the correlations between certain thiopurine drug metabolite levels and therapeutic efficacy and toxicity. The court reasoned that, as construed in the November 2005 summary judgment order, the claims have three steps: (1) administer the drug to a subject; (2) determine metabolite levels; and (3) be warned that an adjustment in dosage may be required. The court stated that the fact that inventors framed the claims as treatment methods does not render the claims patentable. Rather, the court found that the "'administering' and 'determining' steps are merely necessary data-gathering steps for any use of the correlations" and that "as construed, the final step—the 'warning' step (i.e. the 'wherein' clause)—is only a mental step." *Invalidity Opinion*, 2008 WL 878910, at *6. The court noted that the warning step does not require any actual change in dosage and that "it is the metabolite levels themselves that 'warn' the doctor that an adjustment in dosage may be required." *Id.* With this understanding of the claims, the court concluded that the claims recited the correlations between particular concentrations of 6-TG and 6-MMP and therapeutic efficacy or toxicity in patients taking AZA drugs.

Second, the district court found that those correlations were natural phenomena and not patentable

inventions because the correlations resulted from a natural body process. The court stated that the inventors did not "invent" the claimed correlation; rather, "6-TG and 6-MMP are products of the natural metabolizing of thiopurine drugs, and the inventors merely observed the relationship between these naturally produced metabolites and therapeutic efficacy and toxicity." *Invalidity Opinion*, 2008 WL 878910, at *7. Finally, the court determined that "[b]ecause the claims cover the correlations themselves, it follows that the claims 'wholly pre-empt' the correlations." *Id.* at *11. Thus, the court concluded that there was no genuine issue of material fact to be resolved as to whether the patents in suit were directed to statutory subject matter and found by clear and convincing evidence that the claims were invalid under § 101.

On May 16, 2008, the district court entered final judgment, disposing of all the parties' claims and counterclaims. On May 30, 2008, Prometheus timely appealed the district court's grant of summary judgment of invalidity under § 101. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

II. DISCUSSION

A. Standard of Review

We review the district court's grant of summary judgment *de novo*. *AT&T Corp. v. Excel Commc'ns*, 172 F.3d 1352, 1355 (Fed. Cir. 1999). Summary judgment is appropriate if there are no genuine issues of material fact and the moving party is entitled to judgment as a matter of law. *Id.*; Fed. R. Civ. P. 56(c). Whether a patent claim is directed to statutory subject matter is a question of law that we review *de novo*. *AT&T*, 172 F.3d at 1355.

B. Section 101

The issue before us is whether the claims meet the requirements of § 101, so we begin with the text of the statute. Section 101 provides that:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent thereof, subject to the conditions and requirements of this title.

35 U.S.C. § 101. According to § 100(b), "[t]he term 'process' means process, art, or method, and includes a new use of a known process, machine, manufacture, composition of matter, or materials." 35 U.S.C. § 100(b). But, as noted in *In re Bilski*, this definition of process is "unhelpful" because the definition itself uses the term "process." 545 F.3d 943, 951 n.3 (Fed. Cir. 2008) (en banc), *cert. granted*, 129 S. Ct. 2735 (June 1, 2009). Thus, we turn to the case law to guide our understanding of what constitutes statutory subject matter under § 101.

The Supreme Court has construed § 101 broadly, noting that Congress intended statutory subject matter to "include anything under the sun that is made by man." *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). It is well-established, however, that this sweeping statement does not indicate that § 101 is unlimited and embraces every discovery:

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discove-

> ries are "manifestations of . . . nature, free to all men and reserved exclusively to none."

Id. (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). More specifically, the Court has held that a claim to a process is not patent-eligible if it claims "laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981); *see also Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.").

At the same time, it has also been established that "while a claim drawn to a fundamental principle"—*i.e.*, a law of nature, natural phenomenon, or abstract idea—"is unpatentable, 'an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection.'" *Bilski*, 545 F.3d at 953 (quoting *Diehr*, 450 U.S. at 187). The key issue for patentability, then, at least on the present facts, is whether a claim is drawn to a fundamental principle or an application of a fundamental principle. Although this inquiry is hardly straightforward, following the Supreme Court, we articulated in *Bilski* a "definitive test" for determining whether a process is patent-eligible under § 101: "A claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." *Id.* The machine-or-transformation test is a "two-branched inquiry," *i.e.*, the patentee "may show that a process claim satisfies § 101 either by showing that his claim is tied to a

particular machine, or by showing that his claim transforms an article." *Id.* at 961.

The machine-or-transformation test has two further aspects: "the use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility," and "the involvement of the machine or transformation in the claimed process must not merely be insignificant extra-solution activity." *Bilski*, 545 F.3d at 961-62 (citations omitted). "This transformation must be central to the purpose of the claimed process." *Id.* at 962. Thus, in most cases, one cannot ground the transformative nature of a process in a step that is "insignificant extra-solution activity" or merely a "data-gathering step." *See id.* at 963 ("Further, the inherent step of gathering data can also fairly be characterized as insignificant extra-solution activity."). In other words, if steps of a method are included for the purpose of data-gathering rather than being "central" to the purpose of the process, the patentee likely cannot rely on the data-gathering steps to prove that the claimed process is transformative and thus drawn to patentable subject matter. *See id.* at 963 (stating that mere data-gathering will not, "at least in most cases, . . . constitute a transformation of any article").

The Supreme Court has also made clear that the patent eligibility of a claim as a whole should not be based on whether selected limitations constitute patent-eligible subject matter. *See Bilski*, 545 F.3d at 958 (citing *Diehr*, 450 U.S. at 188; *Parker v. Flook*, 437 U.S. 584, 594 (1978)). As noted in *Diehr*, the Court has specifically stated that it is "inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the

analysis." 450 U.S. at 188. Moreover, it is improper to consider whether a claimed element or step in a process is novel or nonobvious, since such considerations are separate requirements set forth in 35 U.S.C. §§ 102 and 103, respectively. *Bilski*, 545 F.3d at 958 (citing *Diehr*, 450 U.S. at 188-91). With this understanding of the present state of the law, we now turn to the parties' arguments in the instant action.

C. Analysis

On appeal, Prometheus argues that the claimed processes satisfy § 101 because they meet both prongs of the machine-or-transformation test articulated in *Bilski*. With respect to the machine prong, Prometheus argues that the patents inextricably rely on numerous machines to process the bodily sample, determine the metabolite levels, and thereby calibrate the proper dose. Prometheus asserts that the district court erred by failing to consider separately the asserted dependent claims, some of which specify measurement through high pressure liquid chromatography, which clearly requires the use of machines. In addition, Prometheus contends that *Bilski*'s use of "machine" in its machine-or-transformation test must be read as shorthand for all patentable subject matter, including compositions of matter. To that end, Prometheus argues that the synthetic drugs used in its treatment methods are compositions of matter, and the claims' central reliance on those drugs is enough to meet the machine-or-transformation test. Alternatively, Prometheus asserts that we should recognize that *Bilski* does not apply where, as here, the treatment methods use synthetic drugs and thus do not recite or wholly preempt any natural phenomenon.

With respect to the transformation prong, Prometheus points to three "transformations" within its claimed process: (1) the first step of administering a synthetic drug transforms the biochemical makeup of the patient's body for the purpose of treating disease; (2) the second step requires the transformation of a bodily sample to determine the created metabolites' concentration levels; and (3) the metabolite levels are transformed into a warning for a doctor to alter the dosage. Regarding the first asserted transformation, Prometheus argues that physical transformations, such as the human body's metabolic reaction to drugs, initiated by human actions and artificial chemical compounds, such as the administration of a thiopurine drug into the body, cannot be unpatentable under *Bilski* simply because they proceed according to natural laws or occur within the human body. Prometheus contends that *everything* proceeds according to natural laws. Regarding the second asserted transformation, Prometheus argues that all of the several methods available to determine the metabolite levels in a bodily sample require a physical transformation of blood or human tissue in order to extract the metabolite and determine its concentration. Finally, regarding the third asserted transformation, Prometheus posits that the ultimate end of the processes is to transform—and improve—the patient's treatment regime while avoiding deadly side effects by transforming the metabolite levels into a warning regarding dosage.

Prometheus then argues that these machines and transformations are central to the invention's purpose of improving a process of treatment and are not confined to extra-solution activity. Prometheus asserts that the district court erred by parsing the steps of the treatment method rather than looking at

the method as a whole, which applies the correlations in concrete physical processes—that Prometheus argues are patentable absent the correlation—to generate useful information. Prometheus contends that adoption of the district court's reasoning would have the effect of eliminating all medical treatment and diagnostic patents, when future medical advances will depend on optimizing treatment based on genetic or other testing.

Mayo responds that the district court properly examined the claims as a whole and correctly determined that they recite the correlations themselves, which are natural phenomena. With respect to the machine prong, Mayo argues that any involvement of machines is insignificant extra-solution activity. Mayo asserts that the step of determining the metabolite levels via an unspecified machine is merely gathering data that is necessary to correlate information. Mayo argues that *Bilski* requires the use of a "particular machine or apparatus" and that no particular machine is involved in Prometheus's process. Mayo contends that Prometheus's reliance on the dependent claims reciting the use of high pressure liquid chromatography is misplaced because choosing to limit the claims to one possible method for performing one of the steps is not sufficient to impart patentability over a natural phenomenon.

Similarly, with respect to the transformation prong, Mayo argues that there is no patentable transformation in the claimed processes. First, Mayo asserts that the administering step is merely a data-gathering step. Mayo points out that the asserted claims do not all include the administering step and thus argues that the administration of the drug cannot be central to the claim. Mayo also contends that

although the thiopurine drugs used in the claims are synthetic, the body's reaction to them is natural, and the drugs themselves were well known. Second, Mayo argues that the determining step is also data-gathering necessary to make any use of the correlations, and the presence of the physical step of transforming clinical samples does not impart patentability to claims to natural correlations. Third, Mayo argues that there is no transformation of data into a warning because the claims do not require any action to be taken to adjust dosage. Under the claim construction argued by Prometheus and adopted by the district court, the final step is a mental step and thus, Mayo argues, the data undergoes no transformation at all.

Furthermore, Mayo asserts that the district court properly determined not only that the claims were to the correlations themselves but that the claims preempt all practical use of the correlations. Post-*Bilski*, Mayo argues that Supreme Court precedent invalidating a claim that wholly preempts a natural phenomenon such that the practical effect is a patent on the phenomenon itself still stands. Mayo contends that because nothing is done with the naturally occurring correlation, the claims cover all implementations resulting from that natural phenomenon and are thus unpatentable. Finally, Mayo argues that invalidating Prometheus's claims will not affect medical treatment methods because infringement of the asserted claims requires no act by a physician at all and no treatment of any disease or condition in a patient. Furthermore, Mayo asserts that upholding the claims under § 101 is dangerous because infringement would occur any time the natural correlation was even considered by a physician.

A number of amici curiae filed helpful briefs on both sides. Those supporting Prometheus argued that the transformation that flows from the use of thiopurine drugs in the patented processes is not "insignificant" post-solution activity but rather a specific and practical application of the correlations in medical treatment. They also argue that the future of personalized medicine will involve knowledge of the physiological or biological significance of biomarkers and how to use them in diagnostic or therapeutic procedures and that patents on those biomarkers should be granted. Those supporting Mayo argue that the district court properly found that the claims impermissibly preempt a natural statistical correlation by asserting exclusive rights over the mere recognition by a treating physician of those correlations. They argue that finding Prometheus's claim to cover patentable subject matter would be granting exclusive rights over mere knowledge of the correlations and would thus interfere with the provision of medical care and with research and quality control in clinical chemistry.

1. *The administering and determining steps are transformative*

We agree with Prometheus that the asserted claims are drawn to statutory subject matter and thus reverse the district court's grant of Mayo's motion for summary judgment of invalidity. As an initial matter, we note that the only issue before us is whether the claims meet the requirements of § 101. This appeal does not raise any questions about lack of novelty, obviousness, or overbreadth, since those are separate statutory requirements for patentability under §§ 102, 103, and 112, respectively. *See Bilski*, 545 F.3d at 958 (citing *Diehr*, 450 U.S. at 188-91).

The proper inquiry under § 101 is whether these methods meet the Supreme Court's machine or transformation test articulated in *Benson* and *Diehr*, and applied in *Bilski*, and, if so, whether the machine or the transformation is central to the purpose of the claims.[2]

We conclude that the methods of treatment claimed in the patents in suit squarely fall within the realm of patentable subject matter because they "transform an article into a different state or thing," and this transformation is "central to the purpose of the claimed process." *See Bilski*, 545 F.3d at 962. The transformation is of the human body following administration of a drug and the various chemical and physical changes of the drug's metabolites that enable their concentrations to be determined. Because the claimed methods meet the transformation prong under *Bilski*, we do not consider whether they also meet the machine prong.

Contrary to the district court, we do not view the disputed claims as merely claiming natural correlations and data-gathering steps.[3] The asserted claims

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[2] We note that the district court did not have the benefit of our *Bilski* decision when deciding the § 101 issue. However, we believe that even prior to *Bilski*, the asserted claims should have been found to be patentable subject matter under the Supreme Court's decisions in *Benson* and *Diehr* and our cases such as *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989), and *In re Abele*, 684 F.2d 902 (CCPA 1982).

[3] In reaching its conclusion, the district court relied heavily on the opinion of three justices dissenting from the dismissal of the grant of certiorari in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) (Breyer, J., dissenting). *See Invalidity Opinion*, 2008 WL 878910, at *8 (discussing the dissent in *Laboratory Corp.* at length and stating that although the dissent "does not have precedential value, the

are in effect claims to methods of treatment, which are always transformative when a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition. More specifically, Prometheus here claimed methods for optimizing efficacy and reducing toxicity of treatment regimes for gastrointestinal and non-gastrointestinal autoimmune diseases that utilize drugs providing 6-TG by administering a drug to a subject. The invention's purpose to treat the human body is made clear in the specification and the preambles of the asserted claims. *See* '623 patent col.2 ll.16-19 ("The present invention provides a method of optimizing therapeutic efficacy of 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder."); *see, e.g.*, *id.* claim 1 ("A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising . . ."); *id.* claim 7 ("A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising . . ."); *id.* claim 22 ("A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease, comprising . . .").

When administering a drug such as AZA or 6-MP, the human body necessarily undergoes a transformation. The drugs do not pass through the body untouched without affecting it. In fact, the transformation that occurs, *viz.*, the effect on the body after metabolizing the artificially administered drugs, is the entire purpose of administering these drugs: the drugs are administered to provide 6-TG, which is thought to be the drugs' active metabolite in the

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Court finds Justice Breyer's reasoning persuasive"). That dissent is not controlling law and also involved different claims from the ones at issue here.

treatment of disease, to a subject. *See* '623 patent col.1 ll.49-51. The fact that the change of the administered drug into its metabolites relies on natural processes does not disqualify the administering step from the realm of patentability. As Prometheus points out, quite literally every transformation of physical matter can be described as occurring according to natural processes and natural law. Transformations operate by natural principles. The transformation here, however, is the result of the physical administration of a drug to a subject to transform—*i.e.*, treat—the subject, which is itself not a natural process. "It is virtually self-evident that a process for a chemical or physical transformation of *physical objects or substances* is patent-eligible subject matter." *See Bilski*, 545 F.3d at 962. The administering step, therefore, is not merely data-gathering but a significant transformative element of Prometheus's claimed methods of treatment that is "sufficiently definite to confine the patent monopoly within rather definite bounds." *Id.* (quoting *Benson*, 409 U.S. at 70).

Mayo is correct that not all of the asserted claims contain the administering step. That omission, which occurs in claims 46 and 53 of the '623 patent, does not diminish the patentability of the claimed methods because the determining step, which is present in each of the asserted claims, is also transformative and central to the claimed methods. Determining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation, for those levels cannot be determined by mere inspection. Some form of manipulation, such as the high pressure liquid chromatography method specified in several of the asserted dependent claims or other modification of the substances to be measured, is necessary to extract the metabolites from a bodily sample and determine

their concentration. As stated by Prometheus's expert, "at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue." Decl. of Dr. Yves Théorêt ¶ 6, *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200 (S.D. Cal. Mar. 29, 2007) (Dkt. No. 528-3). That is clearly a transformation. In fact, Mayo does not dispute that determining metabolite levels in the clinical samples taken from patients is transformative, but argues that this transformation is merely a necessary data-gathering step for use of the correlations. Appellees' Br. 37 ("The 'transformation' of the patient's sample is merely a necessary data-gathering step. . . . [T]he presence of the physical step of transforming clinical samples taken from patients does not impart patentability to Prometheus' claims to the natural correlations."). On the contrary, this transformation is central to the purpose of the claims, since the determining step is, like the administering step, a significant part of the claimed method of treatment. Measuring the levels of 6-TG and 6-MMP is what enables possible adjustments to thiopurine drug dosage to be detected for optimizing efficacy or reducing toxicity during a course of treatment. The determining step, by working a chemical and physical transformation on physical substances, likewise sufficiently confines the patent monopoly, as required by *Bilski*.

2. *The administering and determining steps are not merely data-gathering*

A further requirement for patent-eligibility is ensuring that the involvement of the transformation in Prometheus's claimed process is "not merely insignificant extra-solution activity." *Bilski*, 545 F.3d at 962 (citing *Flook*, 437 U.S. at 590). As made clear from

the discussion above, the administering and determining steps are transformative and are central to the claims rather than merely insignificant extra-solution activity.

The crucial error the district court made in reaching the opposite conclusion was failing to recognize that the first two steps of the asserted claims are not merely data-gathering steps. *See Invalidity Opinion*, 2008 WL 878910, at *6 (finding that "the 'administering' and 'determining' steps are merely necessary data-gathering steps for any use of the correlations"). While it is true that the administering and determining steps gather useful data, it is also clear that the presence of those two steps in the claimed processes is not "merely" for the purpose of gathering data. Instead, the administering and determining steps are part of a treatment protocol, and they are transformative. As explained above, the administering step provides thiopurine drugs for the purpose of treating disease, and the determining step measures the drugs' metabolite levels for the purpose of assessing the drugs' dosage during the course of treatment.

Given the integral involvement of the administering and determining steps in Prometheus's therapeutic methods, this case is easily distinguishable from prior cases that found asserted method claims to be unpatentable for claiming data-gathering steps and a fundamental principle. Perhaps the case that offers the closest comparison is *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989), but the asserted claims found unpatentable in that case are readily distinguished from those in the instant action. In *Grams*, the applicant claimed a process that involved (1) performing a clinical test on individuals and (2) based on the data from that test, determining if an abnormality existed

and determining possible causes of any abnormality by using an algorithm. We found that this process was not drawn to patentable subject matter because the essence of the claimed process was the mathematical algorithm, rather than any transformation of the tested individuals. 888 F.2d at 839-41. More specifically, the *Grams* process was unpatentable because "it was merely an algorithm combined with a data-gathering step," *i.e.*, performing a clinical test. *Bilski*, 545 F.3d at 963. The claims did not require the performing of clinical tests on individuals that were transformative—and thus rendering the entire process patentable subject matter—because the tests were just to "obtain data." *Grams*, 888 F.2d at 840. The patent and thus the court focused only on the algorithm rather than the clinical tests purported to be covered by the claims.

Here, unlike the clinical test recited in *Grams*, the administering and determining steps in Prometheus's claimed methods are not "merely" data-gathering steps or "insignificant extra-solution activity"; they are part of treatment regimes for various diseases using thiopurine drugs. *See Bilski*, 545 F.3d at 963 (discussing *Grams*). As a result, the administering and determining steps are not insignificant extra-solution activity, and the claims are therefore not drawn merely to correlations between metabolite levels and toxicity or efficacy.

3. *The presence of a mental step does not detract from patentability*

We agree with the district court that the final "wherein" clauses are mental steps and thus not patent-eligible per se. However, although they alone are not patent-eligible, the claims are not simply to the mental steps. A subsequent mental step does not,

by itself, negate the transformative nature of prior steps. Thus, when viewed in the proper context, the final step of providing a warning based on the results of the prior steps does not detract from the patentability of Prometheus's claimed methods as a whole. The data that the administering and determining steps provide for use in the mental steps is obtained by steps well within the realm of patentable subject matter. The addition of the mental steps to the claimed methods thus does not remove the prior two steps from that realm.

This analysis is consistent with *In re Abele*, 684 F.2d 902 (CCPA 1982).[4] In *Abele*, a method claim called for the use of X-ray attenuation data, which necessarily involved production, detection, and display with a CAT scan. The method also called for use of an algorithm. We found that the claim was patentable because removal of the algorithm still left all the steps of a CAT scan in the claim; thus, the production and detection could not be considered "mere antecedent steps to obtain values for solving the algorithm. . . . We view the production, detection, and display steps as manifestly statutory subject matter, and are not swayed from this conclusion by the presence of an algorithm in the claimed method." *Id.* at 908. In the instant case, the presence of the mental steps similarly does not detract from the patentability of the administering and determining steps.

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[4] Although *Bilski* reiterated that the *Freeman-Walter-Abele* test is "inadequate" for determining patent-eligibility, *Bilski* spoke approvingly of the analysis regarding the patent-eligible method in *Abele*. *See Bilski*, 545 F.3d at 962-63. Thus, the determination that claim 6 of Abele's patent was patent-eligible subject matter is still good law post-*Bilski*.

As we explained in *Bilski*,

> [I]t is inappropriate to determine the patent eligibility of a claim as a whole based on whether selected limitations constitute patent-eligible subject matter. After all, even though a fundamental principle itself is not patent-eligible, processes incorporating a fundamental principle may be patent-eligible. Thus, it is irrelevant that any individual step or limitation of such processes by itself would be unpatentable under § 101.

545 F.3d at 958 (citations omitted). Such is the case here. Although the wherein clauses describe the mental processes used to determine the need to change the dosage levels of the drugs, each asserted claim as a whole is drawn to patentable subject matter. Although a physician is not required to make any upward or downward adjustment in dosage during the "warning" step, the prior steps provide useful information for possible dosage adjustments to the method of treatment using thiopurine drugs for a particular subject. When viewing the treatment methods as a whole, Prometheus has claimed therapeutic methods that determine the optimal dosage level for a course of treatment. In other words, when asked the critical question of "What did the applicant invent?," *Grams*, 888 F.2d at 839 (citation omitted), the answer is a series of transformative steps that optimizes efficacy and reduces toxicity of a method of treatment for particular diseases using particular drugs.

Furthermore, the district court erred in finding that the claims wholly preempt use of correlations between metabolite levels and efficacy or toxicity. The court reached this conclusion because "the

claims cover the correlations themselves." *Invalidity Opinion*, 2008 WL 878910, at *11. As discussed above, the claims are to transformative methods of treatment, not correlations. The claims cover a particular application of natural processes to treat various diseases, but transformative steps utilizing natural processes are not unpatentable subject matter. Moreover, the claims do not preempt natural processes; they utilize them in a series of specific steps. *See Diehr*, 450 U.S. at 187 ("Their process admittedly employs a well-known mathematical equation, but they do not seek to preempt the use of that equation. Rather, they seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process."). Regardless, because the claims meet the machine-or-transformation test, they do not preempt a fundamental principle. *See Bilski*, 545 F.3d at 954 (characterizing the machine-or-transformation test as "a definitive test to determine whether a process is tailored narrowly enough to encompass only a particular application of a fundamental principle rather than to pre-empt the principle itself"). The inventive nature of the claimed methods stems not from preemption of all use of these natural processes, but from the application of a natural phenomenon in a series of transformative steps comprising particular methods of treatment. *See id.* ("[A] claimed process that transforms a particular article to a specified different state or thing by applying a fundamental principle would not pre-empt the use of the principle to transform any other article, to transform the same article but in a manner not covered by the claim, or to do anything other than transform the specified article."). It is clear that these methods of treatment are § 101 patentable subject matter.

Thus, the claimed methods satisfy all of the requirements under Bilski's transformation prong for patent-eligible subject matter under § 101.

III. CONCLUSION

For the foregoing reasons, we reverse the judgment of the district court and remand to the court with instructions to deny Mayo's motion for summary judgment that the asserted claims are invalid under § 101.

REVERSED and *REMANDED*

APPENDIX D

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

Civil No. 04cv1200 JAH (RBB)

PROMETHEUS LABORATORIES, INC.,
Plaintiff,

v.

MAYO COLLABORATIVE SERVICES dba MAYO MEDICAL LABORATORIES AND MAYO CLINIC ROCHESTER,
Defendants

AND RELATED COUNTERCLAIM.

ORDER

1. GRANTING DEFENDANTS' MOTION FOR SUMMARY JUDGMENT OF PATENT INVALIDITY PURSUANT TO 35 U.S.C. § 101 [Doc. No. 502];

2. DENYING AS MOOT PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT OF NO PATENT EXHAUSTION [Doc. No. 494];

3. DENYING AS MOOT PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT OF DECLARATORY INFRINGEMENT OF PATENT NOS. 6,355,623 AND 6,680,302 [Doc. No. 439];

4. DENYING AS MOOT PLAINTIFF'S MOTION TO STRIKE DECLARATION OF DR. BRUCE BOSTROM [Doc. No. 549]

INTRODUCTION

Now before the Court are three motions for summary judgment filed by the parties, and a motion to strike the declaration of Dr. Bruce Bostrom filed by Plaintiff. The motions have each been fully briefed and oral argument has been entertained. After careful consideration of the pleadings and relevant exhibits presented by the parties, the oral argument presented at the hearing, and for the reasons set forth below, this Court **GRANTS** Defendants' motion for summary judgment of patent invalidity thereby invalidating the patents-in-suit as violative of 35 U.S.C. § 101. Accordingly, Plaintiff's motions for summary judgment of no patent exhaustion and for declaratory judgment of infringement are **DENIED as moot**, and will not be addressed herein. Plaintiff's motion to strike the declaration of Dr. Bruce Bostrom is also **DENIED as moot.**

BACKGROUND

A. Factual Background

Plaintiff, Prometheus Laboratories ("Plaintiff" or "Prometheus"), is the exclusive licensee of two patents: U.S. Patent Nos. 6,355,623 ("the '623 patent") and 6,680,302 ("the '302 patent") (collectively "the patents-in-suit"). The patents-in-suit involve measurements of the level of certain metabolites in the blood of patients taking thiopurine drugs, including the anti-Crohn's disease drug azathioprine ("AZA"), for treatment of either gastrointestinal autoimmune diseases or non-gastrointestinal autoimmune diseases. The patented test provides a means to measure the level of two metabolites: 6-thioguinine ("6-TG") and 6-methylmercaptopurine ("6-MMP"), which, ac-

cording to the patent, indicates that an adjustment in drug dosage may be required at metabolite levels "greater than about 400" and "greater than about 7000," respectively, in order to avoid toxic side effects.

Defendants, Mayo Collaborative Services dba Mayo Medical Laboratories and Mayo Clinic Rochester (collectively "Defendants" or "Mayo") developed a test ("the accused test") to measure the same metabolites but using different levels, 450 6-TG and 5700 6-MMP. In June 2004, Defendants announced they intended to begin use of their accused test, offering it for sale to potential purchasers, but the announcement was later rescinded. The instant lawsuit followed.

B. Procedural History

Plaintiff filed its patent infringement complaint on June 15, 2004. On January 27, 2005, Defendants filed a motion for summary judgment seeking a declaration of non-infringement, which this Court denied on November 22, 2005. Doc. No. 227. Plaintiff filed a cross-motion for summary judgment, seeking a judicial declaration that Defendants' accused test literally infringes Claim 7 of the '623 patent, which this Court granted in its November 22, 2005 order.[1] Defendants filed a motion seeking relief from the

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[1] In its November 22, 2005 order, this Court construed the following terms contained in the patents-in-suit: (1) "greater than about 400" was construed to mean "any level above 340 to 460"; and "indicates a need" was construed to mean "a warning that an adjustment in dosage may be required." Doc. No. 227 at 18.

Court's November 22, 2005 order, which the Court denied. Doc. Nos. 230 and 260.

On December 13, 2005, this Court granted both parties' motions to amend their respective pleadings. Doc. No. 234. Plaintiff filed a first amended complaint ("FAC") on December 22, 2005. Doc. No. 236. Defendants filed an answer to the FAC, along with amended counterclaims, on January 13, 2006. Doc. No. 241. On April 14, 2006, the parties stipulated to the filing of a second amended complaint ("SAC"). Doc. No. 267.

Three separate motions for summary judgment followed. On January 9, 2007, Plaintiff filed a motion for summary judgment of no patent exhaustion. Doc. No. 494. Defendants filed an opposition to Plaintiff's motion on February 22, 2007. Doc. No. 519. Plaintiff filed a reply on March 1, 2007. Doc. No. 529.

Defendants filed a motion for summary judgment of patent invalidity under 35 U.S.C. § 101 on January 29, 2007.[2] Doc. No. 502. Plaintiff filed an opposition to Defendants' motion on February 28, 2007. Doc. No. 528. Defendants filed their reply on March 9, 2007. Doc. No. 542. Included in Defendants' reply brief was a declaration by Dr. Bruce Bostrom. Plaintiff subsequently filed a motion to strike Dr. Bostrom's declaration. Doc. No. 549. Defendants filed an opposition to Plaintiff's motion and Plaintiff filed a reply. Doc. Nos. 566 and 568.

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[2] Defendants also filed, on January 25, 2007, a motion to strike Plaintiff's jury demand. Doc. No. 501. Because Plaintiff did not oppose the motion, the Court subsequently granted the motion and struck the jury demand. Doc. No. 546.

On March 8, 2007, Plaintiff filed a motion for summary judgment of declaratory judgment of infringement. Doc. No. 539. Defendants filed an opposition to Plaintiff's motion on April 12, 2007. Doc. No. 561. Plaintiff filed a reply on April 19, 2007. Doc. No. 565.

The Court rescheduled the motion hearing on the first summary judgment motions so that all motions (including the motion to strike the declaration of Bruce Bostrom) could be heard on the same day, May10, 2007, and set a briefing schedule for the remaining pleadings. On May 10, 2007, after all the motions were fully briefed, this Court heard oral argument from the parties and took all four motions under submission.

On October 1, 2007, while the motions were still under submission, the parties filed a joint application requesting permission to submit additional briefing on two recently decided Federal Circuit cases: *In re Comiskey*, 499 F.3d 1365 (Fed. Cir. 2007), and *In re Nuijten*, 500 F.3d 1346 (Fed. Cir. 2007). Doc. No. 584. The Court granted the request, and on October 26, 2007, Defendants submitted a brief regarding *Comiskey* and *Nuijten*. Doc. No. 586. Plaintiff submitted its own brief on November 9, 2007. Doc. No. 588. Defendants then requested, and were granted, leave to file a reply brief, which they filed on November 19, 2007. Doc. No. 590, Exhibit A. Plaintiff then submitted a sur-reply brief on November 30, 2007. Doc. No. 593.

DISCUSSION

Defendants have moved for summary judgment on the grounds that the patents-in-suit are invalid

because they impermissibly claim unpatentable subject matter under 35 U.S.C. § 101. Specifically, Defendants contend that the patents impermissibly claim natural phenomena – the correlations between thiopurine drug metabolite levels on the one hand and therapeutic efficacy and toxicity on the other – and the claims "wholly pre-empt" use of the natural phenomena. *See* Doc. No. 502 at 11-12.

A. Legal Standards

1. Summary Judgment

Summary judgment is appropriate under Rule 56(c) of the Federal Rules of Civil Procedure where the moving party demonstrates the absence of a genuine issue of material fact and entitlement to judgment as a matter of law. Fed. R. Civ. P. 56(c); *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986). A fact is material when, under the governing substantive law, it could affect the outcome of the case. *See Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986); *Freeman v. Arpaio*, 125 F.3d 732, 735 (9th Cir. 1997). A dispute about a material fact is genuine if "the evidence is such that a reasonable jury could return a verdict for the nonmoving party." *Anderson*, 477 U.S. at 248.

A party seeking summary judgment always bears the initial burden of establishing the absence of a genuine issue of material fact. *See Celotex*, 477 U.S. at 323. The moving party may satisfy this burden in two ways: (1) by presenting evidence that negates an essential element of the nonmoving party's case or (2) by demonstrating that the nonmoving party failed to make a showing sufficient to establish an element essential to that party's case on which that party will

bear the burden of proof at trial. *Id.* at 322-23. "Disputes over irrelevant or unnecessary facts will not preclude a grant of summary judgment." *T.W. Elec. Serv., Inc. v. Pacific Elec. Contractors Ass'n*, 809 F.2d 626, 630 (9th Cir. 1987). "The district court may limit its review to the documents submitted for purpose of summary judgment and those parts of the record specifically referenced therein." *Carmen v. San Francisco Unified Sch. Dist.*, 237 F.3d 1026, 1030 (9th Cir. 2001). Therefore, the court is not obligated "to scour the record in search of a genuine issue of triable fact." *Keenan v. Allen*, 91 F.3d 1275, 1279 (9th Cir. 1996) (citing *Richards v. Combined Ins. Co.*, 55 F.3d 247, 251 (7th Cir. 1995)). If the moving party fails to discharge this initial burden, summary judgment must be denied and the court need not consider the nonmoving party's evidence. *See Adickes v. S.H. Kress & Co.*, 398 U.S. 144, 159-60 (1970).

If the moving party meets the initial burden, the nonmoving party cannot defeat summary judgment merely by demonstrating "that there is some metaphysical doubt as to the material facts." *Matsushita Elec. Indus. Co., Ltd. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986); *see also Anderson*, 477 U.S. at 252 ("The mere existence of a scintilla of evidence in support of the nonmoving party's position is not sufficient."). Rather, the nonmoving party must "go beyond the pleadings and by her own affidavits, or by the depositions, answers to interrogatories, and admissions on file, designate specific facts showing that there is a genuine issue for trial." *Celotex*, 477 U.S. at 324 (quoting Fed. R. Civ. P. 56(e)) (internal quotations omitted).

When ruling on summary judgment, the court may not make credibility determinations, and inferences to be drawn from the facts must be viewed in the light most favorable to the party opposing the motion. *Masson v. New Yorker Magazine*, 501 U.S. 496 (1991); *see also Anderson*, 477 U.S. at 249, *Matsushita*, 475 U.S. at 587.

2. Section 101

Defendants move for summary judgment for patent invalidity under 35 U.S.C. § 101. Section 101 provides that:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.[3]

35 U.S.C. § 101

The Supreme Court has construed section 101 broadly, observing that Congress intended statutory subject matter to include "anything under the sun that is made by man." *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). However, it is well settled that there are qualifications to the apparent sweep of this statement. In *Chakrabarty*, the Supreme Court explained that:

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[3] The word "process" is defined in 35 U.S.C. § 100(b): "The term 'process' means process, art, or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material."

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'

447 U.S. at 309 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). Accordingly, the Supreme Court has specifically excluded from patentable subject matter: "laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). As the Court explained, "[p]henomena of nature, though just discovered, mental processes and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

In assessing patentability under section 101 in the context of method patents, the Supreme Court has explained that a method patent is not invalid "simply because it contains a law of nature or a mathematical algorithm." *Parker v. Flook*, 437 U.S. 584, 590 (1978). But, if the claim "recites" a law of nature or a mathematical algorithm, the court must analyze whether the claim is seeking patent protection for the phenomenon "in the abstract" or whether the claim implements a natural phenomenon "in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect." *Diehr*, 450 U.S. at 191. Thus, where the claim "wholly pre-empts" all uses of the natural phenomenon or abstract idea such that the

"practical effect is a patent on the [phenomenon] itself' the claim is invalid under section 101. *Benson*, 409 U.S. at 71-72; *see also Diehr*, 450 U.S. at 187.

It is also important to note that "[p]atentability does not depend on which form the claim takes." *Nuijten*, 500 F.3d at 1362. As the Supreme Court has repeatedly explained, an "unpatentable principle" will not transform into a "patentable process" simply by adding conventional method steps. *Flook*, 437 U.S. at 588-90; *see also Diehr*, 450 U.S. at 191-92. If such were the case, "the determination of patentable subject matter [would] depend simply on the draftman's art." *Id.* at 593.

Whether a patent claim is invalid for failure to comply with section 101 is a question of law appropriate for summary judgment. *AT&T Corp. v. Excel Comm. Inc.*, 172 F.3d 1352, 1355 (Fed. Cir. 1999). When conducting the section 101 analysis, the claims must be examined "as a whole." *Diehr*, 450 U.S. at 188. The Supreme Court has specifically cautioned that it is "inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Id.* at 188. Moreover, it is improper to consider the "novelty" of an element or step in a process claim. *Id.* at 188-89. Instead, novelty is a separate requirement set forth in 35 U.S.C. § 102.

Finally, Defendants who are challenging the validity of the claims of the patents-in-suit must show that the claims at issue are invalid by clear and convincing evidence. *Minnesota Mining and Mfg. Co. v. Chemque Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002). Thus, Defendants must show by clear and convincing evidence that the claims at issue (1) recite a "natural

phenomenon," and (2) "wholly pre-empt" use of said phenomenon.

B. Analysis

Defendants contend that (1) the patents-in-suit claim the "correlation between the recited metabolite levels and therapeutic efficacy and/or toxicity" which is an unpatentable "natural, observable phenomenon"; and (2) the patents impermissibly preempt use of the correlation. Doc. No. 502 at 11, 13.

1. Recitation of Unpatentable Natural Phenomena

The first step in determining patentability under section 101 is to determine whether the claims "recite" a "natural phenomenon." *See Diehr*, 450 U.S. at 187; *see also In re Meyer*, 688 F.2d 789, 795 (C.C.P.A. 1982). For the reasons set forth below, this Court finds the patents-in-suit claim the correlations between certain thiopurine drug metabolite levels and therapeutic efficacy and toxicity, and said correlations are natural phenomena.

a. The Patents-in-Suit Recite the Correlations

Defendants assert that the patents-in-suit recite the correlation between thiopurine drug metabolite levels on the one hand and therapeutic efficacy and toxicity on the other. *See* Doc. No. 502 at 11-12. According to Defendants, the patents contain these correlations in the "wherein" clauses at the end of each claim. Though the "wherein" clauses are preceded by two steps – (1) "administering" a drug and (2) "determining" metabolite levels – Defendants argue that because both these steps have been performed in the

prior art for decades, and each is a necessary step to making any use of metabolite levels, the claims cover the correlations themselves. Plaintiff counters that the claims at issue do not "recite" the correlations, rather the claims recite treatment methods which do not run afoul of section 101. *See* Doc. No. 528 at 1 n.1, 13.

Plaintiff has framed the patents-in-suit as treatment methods in that the claims purport to cover a "method for optimizing therapeutic efficacy" and/or "reducing toxicity" in patients taking AZA drugs for treatment of either gastrointestinal autoimmune diseases or nongastrointestinal autoimmune diseases. For example, Claim 1 of the '302 patent states:

1. A method of optimizing therapeutic efficacy for treatment of an immune mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder wherein the levels of 6-thioguanine less than about 230 pmol per 8x108 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the levels of 6-thioguanine greater than about 400 pmol per 8x108 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

In the summary judgment order filed November 22, 2005, this Court construed the "indicates a need" language found in the "wherein" clause to mean

"when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required." Doc. No. 227 at 17. As construed, the claims have three steps: (1) administer the drug to a subject; (2) determine metabolite levels; and (3) be warned that an adjustment in dosage may be required.

However, the fact that the inventors have framed the claims as "treatment methods" does not make the claims patentable. Indeed, "one can reduce any process to a series of steps. The question is what those steps embody." *Lab. Corp. of Am. Holdings v. Metabolite, Inc.*, 126 S.Ct. 2921 (2006) (Breyer, J., dissenting from dismissal of certiorari) (emphasis in original); *see also In re Grams*, 888 F.2d 835, 839 (Fed. Cir. 1989) (explaining that the critical question is: "What did applicants invent?") (quoting *In re Abele*, 684 F.2d 902, 907 (C.C.P.A. 1982)).

Here, a careful review of the claims of the patents-in-suit reveals that the steps embody only the correlations themselves. First, the "administering" and "determining" steps are merely necessary data-gathering steps for any use of the correlations. However, an "unpatentable principle" will not transform into a "patentable process" simply by adding conventional method steps. *Flook*, 437 U.S. at 588-90; *accord Meyer*, 688 F.2d at 794 ("[data-gathering] step[s] cannot make an otherwise nonstatutory claim statutory"). Thus, the Court must look to the third step to determine what the applicants claim to have invented. However, as construed, the final step – the "warning" step (i.e. the "wherein" clause) – is only a mental step. That is, the "warning" step does not require that dosage be adjusted, or any other action.

Indeed, contrary to Plaintiff's assertion, the "warning step" does not require that the doctor (or any person) "provide" a warning. *See* Doc. No. 528 at 14. Rather, it is the metabolite levels themselves that "warn" the doctor that an adjustment in dosage may be required.

Thus, the claims include only two active steps: "administering" the drug and "determining" metabolite levels, which are merely data-gathering steps; plus the additional mental step that the doctor be warned (by the metabolite levels) that an adjustment in dosage may be required. Therefore, the claims recite the correlations themselves. That is, what the inventors claim to have discovered is that particular concentrations of 6-TG and 6-MMP correlate with therapeutic efficacy and toxicity in patients taking AZA drugs.

b. The Correlations Are Natural Phenomena

Because the patents-in-suit claim the correlations, the Court must next determine whether the correlations are "natural phenomena." Defendants argue that the correlation between thiopurine drug metabolite levels and therapeutic efficacy and toxicity results from innate metabolic activity in the human body, and the correlations are therefore "natural phenomena." Doc. No. 542 at 5.[4] Plaintiff coun-

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[4] Doc. No. 542 is Defendants' reply in support of their motion for summary judgment of patent invalidity. Defendants submitted, in support of their reply brief, the declaration of Dr. Bruce Bostrom, which declaration Plaintiff separately moves to strike. *See* Doc. No. 549. Specifically, Plaintiff contends (1) Dr. Bostrom presents purely expert opinion but was not disclosed as an expert witness during discovery; (2) to the extent Dr. Bo-

ters that the claimed correlations cannot be natural phenomena because the correlations would not have existed without the intervention of man-made drugs.[5] Doc. No. 528 at 8.

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strom's declaration is factual, Defendants also never disclosed him as a fact witness during discovery; and (3) Defendants should have presented the declaration with their moving papers and the late presentation is prejudicial to Plaintiff. Plaintiff argues that the declaration should be stricken for any of these reasons. *See id.* In the alternative, if the Court does not strike the declaration, Plaintiff requests it be permitted to file a sur-reply and attaches a proposed sur-reply to the motion as an exhibit. *See id.*, Exh. A. Defendants filed an opposition to Plaintiff's motion to strike and Plaintiff filed a reply to Defendants' opposition. However, this Court has not considered Dr. Bostrom's declaration in deciding the instant motion and, therefore, Plaintiff's motion to strike is DENIED as moot.

[5] Plaintiff contends "Congress has not excluded treatment methods or discovered correlations occurring from a man-made drug from patent protection and, in fact, has rejected proposed legislation to make treatment methods unpatentable. *Id.* (citing Morgan Decl., Exh. 11 (1995 Cong. U.S. HR 1127 (104th Congr., 1st Sess.)). The bill proposed that "a patent may not be issued for any invention or discovery of a technique, method, or process for performing a surgical or medical procedure, administering a surgical or medical therapy, or making a medical diagnosis, except that if the technique, method, or process is performed by or as a necessary component of a machine, manufacture, or composition of matter or improvement thereof which is itself patentable subject matter, the patent on such machine, manufacture, or composition of matter may claim such technique, method, or process." 1995 Cong. HR 1127 (104th Congr., 1st Sess.). However, Defendants, in reply, urge the Court to ignore this irrelevant point because the failure to enact this legislation provides no support for the validity of the claims at bar. Doc. No. 542 at 14. This Court agrees with Defendants. The fact that Congress rejected legislation making treatment methods unpatentable is irrelevant, and not an appropriate basis for a determination of Congressional intent.

This Court finds that there can be little doubt that the claimed correlations are "natural phenomena." According to Plaintiff's own expert, Dr. Bloomfield, "the key therapeutic aspect of such thiopurine drugs is that they are converted *naturally* by enzymes within the patient's body to form an agent that is therapeutically active." Doc. No. 542, Exh. R ¶ 15 (emphasis added). Moreover, Dr. Seidman, one of the patents' inventors, concedes that the inventors merely observed these natural correlations by studying a "database of patient's information" which included patients taking 6-MP drugs. *See* Doc. No. 502, McClenahan Decl., Exh. K at 103-105. Dr. Seidman further testified that he believes the correlation still exists in the current patient population. Thus, the inventors of the patents-in-suit did not "invent" the claimed correlation. Rather, 6-TG and 6-MMP are products of the natural metabolizing of thiopurine drugs, and the inventors merely observed the relation ship between these naturally produced metabolites and therapeutic efficacy and toxicity.

The case law supports this conclusion. In *Funk Bros.*, for example, an inventor discovered a previously unknown feature of certain types of bacteria – that they could, "by certain methods of selection and testing, be isolated and used in mixed cultures" without inhibiting the properties of one another. 333 U.S. at 130. The patents at issue in that case claimed an inoculant for crops comprising a combination of these bacteria. *Id.* at 128, n.1. The Supreme Court held the claims invalid. The Court explained that the inventor did not "create" the "state of inhibition or non-inhibition in bacteria." *Id.* at 130. Rather, "[t]heir qualities are the work of nature." *Id.*

The same is true in the present case. The inventors here did not "create" the correlation between thiopurine drug metabolite levels and therapeutic efficacy and toxicity. Instead, the correlation results from a natural body process, which as the inventors concede, was pre-existing in the patient population, and it exists in the patient population today. Thus, just as in *Funk Bros.*, the claimed correlations are "the work of nature."

The facts of the present case are also similar to those of *Lab. Corp.*[6] The patent in *Lab. Corp.* claimed a method of measuring the level of an amino acid, called homocysteine, in the blood, which correlated with a deficiency in two vitamins: cobalamin and folate. *Lab. Corp.*, 126 S.Ct. at 2923-24. At the trial level, Lab. Corp. (the alleged infringers) did not argue invalidity under section 101, and instead based their invalidity arguments on other grounds. *See Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354 (Fed. Cir. 2004). The Federal Circuit, on appeal, rejected the invalidity arguments without addressing section 101. *Id.* The Supreme Court granted certiorari in order to determine whether the claim was invalid on the grounds that it improperly

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[6] The Court takes note of Plaintiff's objections to the *Lab Corp.* opinion, namely that the opinion is not binding precedent and the dissent was issued on an incomplete record. And although at the time of the hearing on Defendants' motion this Court was not of the opinion that *Lab. Corp.* is directly relevant, after further review, this Court now finds that while *Lab. Corp.* does not hold precedential value, its reasoning is persuasive and relevant. A review of the case law in this area reveals that *Lab Corp.* is the case that is most factually similar to the present case. Thus, the Court would be remiss to ignore the case entirely.

seeks to "claim a monopoly over a basic scientific relationship," Pet. for Cert. i, namely, the relationship between homocysteine and vitamin deficiency. *Lab. Corp.*, 126 S.Ct. at 2922. However, the Court never reached the issue because the writ was subsequently dismissed as improvidently granted apparently because the issue was not raised below. *Id.*

Nonetheless, Justice Breyer (joined by Justices Stevens and Souter), dissented from the dismissal of certiorari, and presented a lengthy dissenting opinion explaining why the patent should be found invalid under section 101. *See id.* at 2922-29. Justice Breyer, after reviewing the relevant cases in the subject area, stated:

> Even were I to assume (purely for argument's sake) that [the claim] meets certain general definitions of process patentability, however, it still fails the one at issue here: the requirement that it not amount to a simple natural correlation, *i.e.*, a 'natural phenomenon' . . .
>
> At most, respondents have simply described the natural law at issue in the abstract patent language of a 'process.' But they cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge. One might, of course, reduce the 'process' to a series of steps, *e.g.*, Step 1: gather data; Step 2: read a number; Step 3: compare the number with the norm; Step 4: act accordingly. But one can reduce *any* process to a series of steps. The question is what those steps embody. And here, aside from the unpatented test, they embody only the correlation between homocysteine and vi-

> tamin deficiency that the researchers uncovered. In my view, that correlation is an unpatentable 'natural phenomenon' and I can find nothing in [the claim] that adds anything more of significance.

Id. at 2928 (Breyer, J., dissenting from dismissal of certiorari) (internal citations omitted) (emphasis in original).

Although this Court notes that the dissent in *Lab. Corp.* does not have precedential value, the Court finds Justice Breyer's reasoning persuasive. Indeed, the claims in the patents-in-suit are clearly analogous to the claim in *Lab. Corp.* The claim at issue in *Lab Corp.* comprised two steps: "[(1)] assaying a body fluid for an elevated level of total homocysteine; and [(2)] correlating an elevated level of total homocysteine in said body fluid with deficiency of cobalamin or folate." *Id.* at 2924. The "assaying" step in *Lab Corp.* is akin to the "administering" and "determining" steps in the claims of the patents-in-suit as both are necessary steps for any use of the correlations. Similarly, *Lab Corp.'s* "correlating" step is akin to the "wherein" clause in the present case as both recite the claimed correlation. Thus, the same reasoning that led Justice Breyer to conclude that the correlation between elevated homocysteine levels and deficiency of cobalamin or folate is a natural phenomenon supports the finding that the correlation between thiopurine drug metabolite levels and therapeutic efficacy and toxicity is a natural phenomenon.

Plaintiff argues, however, that the claimed correlations cannot be found to be natural phenomena because the correlations would not have existed without the intervention of man-made drugs. Plaintiff

points out that thiopurine drugs are man-made drugs. Doc. No. 528 at 10. When these drugs are introduced into the body, they metabolize "to form an 'active metabolite' which then treats the patient's disease." *Id.* at 10-11. Thus, according to Plaintiff, because "the 6-TG and 6-MMP metabolites do not naturally exist in the body . . . [and would not exist] but for the administration of a man-made drug" the claimed correlations cannot be deemed "natural phenomena." *Id.* at 11. In support of this argument, Plaintiff cites to cases where courts have upheld as patentable claims involving the efficacy of man-made compositions, *see e.g.*, *Merck & Co. v. Teva Pharm., Inc.*, 347 F.3d 1367, 1369, 1372 (Fed. Cir. 2003), as well as claims involving portions of genes and proteins (which do not exist in nature). *See e.g.*, *Fiers v. Revel*, 984 F.2d 1164, 1166, 1172 (Fed. Cir. 1993).

However, in the Court's view, the cases Plaintiff cites do not support the patentability of the claims because the claims in the present case, unlike the claims in the cases cited by Plaintiff, do not cover the man-made compositions themselves or use of man-made compositions to treat inflammatory bowel disease or autoimmune diseases. In *Merck*, for example, the claims covered a method for treating osteoporosis through the administration of a bisphosphonic acid, a man-made composition. 347 F.3d at 1369. The claims at issue in that case specifically covered use of the acid in the treatment method. *Id.* at 1369. This contrasts with the present case where the claims cover the correlations themselves, rather than use of the man-made composition to treat the targeted disease, as this Court has already found. Because the patents-in-suit claim the correlations, the relevant inquiry is whether the correlations are "man-made,"

not whether a man-made drug was used to produce the correlation.[7]

Again, the present case is most similar to *Funk Bros.* In that case, the claimed combination of bacteria was "man-made." That is, the claimed strains of bacteria had to be manually isolated and mixed, and therefore would not exist in nature without human intervention. 333 U.S. at 130. Despite this human intervention, the claim was nonetheless unpatentable under section 101. *Id.* at 132. As such, per *Funk Bros.*, claims do not gain patentability simply by including man-made compositions. Thus, the patents-in-suit do not gain patentability solely by virtue of the fact that man-made drugs are used in connection with the claimed correlation.

The recent Federal Circuit case, *Nuijten*, further supports this finding. *Nuijten* concerned a patent application which disclosed "a technique for reducing distortion induced by the introduction of 'watermarks' into signals." 500 F.3d at 1348. The court analyzed whether *Nuijten's* "signal claim" fell within any of the four statutory classes of patentable subject matter: process, machine, manufacture, or composition of matter. *Id.* at 1353. Ultimately, the court concluded that the claim was unpatentable because it did not fit within any of the statutory categories. *Id.* at 1357. In ruling that the claim was not a "manufac-

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[7] This same reasoning makes *Fiers* inapposite as well. Plaintiff cites to *Fiers* merely because it involved man-made compositions – purified DNA. Plaintiff argues that if claims to portions of genes and proteins (which do not exist in nature) are not "natural phenomenon" then the correlations cannot be "natural phenomenon" either. Doc. No. 528 at 11.

ture" the court explained that the claimed signal was "man-made, in the sense of having been encoded, generated, and transmitted by artificial means," however "artificiality is insufficient by itself to render something a 'manufacture.'" *Id.* at 1356. Thus, the fact that the claimed signal was "man-made" did not automatically make the claim patentable. To the contrary, although the claimed signal was "man-made," it was still unpatentable.[8]

In short, the correlation between particular 6-TG and 6-MMP metabolite levels and therapeutic efficacy and toxicity is not an "invention." Rather, 6-TG and 6-MMP are products of the natural metabolizing of thiopurine drugs, and the inventors merely discovered the relationship between these naturally produced metabolites and therapeutic efficacy and toxicity.

2. Preemption

Because the Court has determined that the claims of the patents-in-suit recite a natural pheno-

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[8] Plaintiff's argument that *Nuijten* is "irrelevant to the present case" is to no avail. Doc. No. 588 at 25. Plaintiff would have the Court believe that the *Nuijten* holding "had nothing to do with whether or not the claimed subject matter was 'man-made.'" *Id.* This is incorrect. The Federal Circuit's finding that the claimed signal was "man-made" and yet not a "manufacture," was one of several reasons why the court ultimately determined that the claim was unpatentable. Thus, *Nuijten* confirms that claims do not gain patentability simply because they incorporate something that is "man-made." Finally, Plaintiff's argument that *Nuijten* is irrelevant because the present case recites "a process" is similarly unpersuasive. As the Court already found, although the patents-in-suit are framed as "method claims," they claim the correlations themselves.

menon, the Court must next determine whether the claims "wholly pre-empt" use of the natural phenomenon such that the "practical effect is a patent on the [phenomenon] itself." *Benson*, 409 U.S. at 71-72; *see also Diehr*, 450 U.S. at 187. Defendants argue that because the "administering" and "determining" steps are necessary to using the correlations, Plaintiff's claims "wholly pre-empt" use of the correlations in violation of Supreme Court precedent, and are thus invalid under section 101. Doc. No. 502 at 13-14. In opposition, Plaintiff argues first, that the relevant tests is the alternative "transformation/results" test not the preemption test. *See* Doc. No. 528 at 7-8. Second, even if the Court applies the preemption test, the claims do not "wholly pre-empt" all uses of the correlations. This Court finds that (a) the preemption test is the relevant test and (b) Plaintiff's claims "wholly pre-empt" use of the correlations.

a. The Preemption Test

The case law is clear, if a claim that recites unpatentable subject mater "wholly pre-empts" all practical use of the unpatentable subject matter, the claim is invalid under section 101. *Benson*, 409 U.S. at 71-72; *see also Diehr*, 450 U.S. at 187. *Benson* involved an attempt to patent "a method of programming a general-purpose digital computer to convert signals from binary-coded decimal form into pure binary form." *Id.* at 65. The conversion was achieved through use of an algorithm, defined as "[a] procedure for solving a given type of mathematical problem." *Id.* at 67. The claims "were not limited to any particular art or technology, to any particular apparatus or machinery, or to any particular end use." *Id.* at 64. The Supreme Court concluded that because

the claimed process "has no substantial practical application except in connection with a digital computer" the patent "would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself." *Id.* at 71-72. For this reason, the Court held the patent invalid. *Benson* is binding Supreme Court precedent, and the preemption test articulated therein is clearly applicable to the present case.

Moreover, contrary to Plaintiff's contention, Defendants need not meet the additional burden of showing that the claims do not "transform" an article or physical object to a different state or thing and/or do not produce a "useful, concrete and tangible result." Doc. No. 528 at 7-8 (citing *AT&T*, 172 F.3d at 1357-58). The case law in this area reveals that the additional showing urged by Plaintiff is not required. In *Flook*, for example, the Supreme Court did not even mention the alternative transformation/result standard, and instead focused on whether the claims "wholly pre-empt" all uses of the natural phenomenon. 437 U.S. at 589-90.[9] Also, although *Comiskey* mentions the "transformation" test, it does so in regards to process patents reciting algorithms or abstract concepts in claims directed to industrial processes. Such claims clearly differ from those in the present case. The *Comiskey* court specifically noted that "process claims not limited to claiming an

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[9] During oral argument, Plaintiff argued that *Flook* was "overruled" by the Supreme Court in *Diehr*. *See* May 10, 2007 Hearing Transcript at 38:14-24. However, in *Comiskey*, the Federal Circuit repeatedly cited *Flook* and also explained the case. 499 F.3d at 1371, 1375, 1376, 1377-78. This confirms that *Flook* remains good law.

abstract concept or algorithm (i.e., a mental process) *may not be subject to the same requirements.*" 499 F.3d at 1377 n.12 (emphasis added).

As for the "useful, concrete and tangible result" standard, the Supreme Court has never applied that standard. *See Lab. Corp.*, 126 S. Ct. at 2928 (pointing out that the Supreme Court has never held "that a process is patentable if it produces a 'useful, concrete, and tangible result' . . . and if taken literately, the statement would cover instances where this Court has held the contrary") (Breyer, J., dissenting). Furthermore, while the Federal Circuit has applied the standard, it has always done so in the context of computer-related inventions involving algorithms for data manipulation. *See e.g.*, *State Street Bank and Trust Co. v. Signature Fin. Group, Inc.*, 149 F.3d 1368 (Fed. Cir. 1998).

Thus, this Court finds that the claims at issue are not subject to either the transformation test or the "useful, concrete and tangible" result test.

b. The Claims "Wholly Pre-empt" the Use of the Correlation

Defendants argue that the claims "wholly pre-empt" use of the correlation because the only practical use of the correlation is in drug treatment for gastrointestinal autoimmune diseases and non-gastrointestinal autoimmune diseases, and anyone seeking to employ the correlation must conduct the only active steps recited in the claims – administer the drug and determine metabolite levels. Doc. No. 502 at 13-15. This Court agrees.

This Court has already found that the claims recite the correlations. Specifically, the Court has found that the "administering" and "determining" steps are merely necessary data gathering steps for any use of the correlations, and the "warning" step is only a mental step whereby the metabolite levels warn the doctor that an adjustment in dosage may be required. Thus, the claims cover the correlations themselves. That is, what the inventors claim to have discovered is that particular concentrations of 6-TG and 6-MMP correlate with therapeutic efficacy and/or toxicity in patents taking AZA drugs. Because the claims cover the correlations themselves, it follows that the claims "wholly pre-empt" the correlations.

For the same reason, the Court rejects Plaintiff's argument that it may preclude others from using the correlations "in conjunction with all the other steps in their claimed process." Doc. No. 528 at 19 (citing *Diehr*, 450 U.S. at 187; *Arrhythmia Research Tech., Inc. v. Corazoniz Corp.*, 958 F.2d 1053, 1059 (Fed. Cir. 1992)). Again, the only "other steps" recited in

the claims are the "administering" and "determining" steps, which are necessary data-gathering steps. And, the inclusion of such steps cannot "transform an unpatentable principle into a patentable process." *Diehr*, 450 U.S. at 191-192.

The Court also finds Plaintiff's supposed examples of other permissible uses of the correlations unavailing. Doc. No. 528 at 19-20. First, the law does not require that every conceivable use be preempted to invalidate the claim. Rather, it is enough that the unpatentable subject matter recited in the claims has "no substantial practical application" outside the context of the claims. *Benson*, 409 U.S. at 71-72. In *Benson*, the Court found that the mathematical formula involved in that case had "no substantial practical application except in connection with a digital computer." *Id.* Thus, a patent which claimed "a method of programming a general-purpose digital computer to convert signals from binary-coded decimal form into pure binary form" through the use of a mathematical formula would "wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself." *Id.* at 65, 71-72. The same is true in the present case. Because the correlations have "no substantial practical application" outside of the treatment for immune mediated gastrointestinal disorders and autoimmune diseases, it does not matter that uses outside of this context are not foreclosed.

Second, the alternate uses cited by Plaintiff as not being preempted do not change the fact that the "practical effect" of the patent would be a "patent on the [phenomenon] itself." *Id.* at 72. Plaintiff outlines six possible uses not foreclosed by the claimed me-

thods: (1) use in research; (2) for diseases other than autoimmune or gastrointestinal diseases;[10] (3) use when results are given in units other than red blood cells; (4) building upon the correlations; (5) publishing articles in scientific journals concerning the correlations; and (6) testing and determining metabolite levels so long as no warning is given. Doc. No. 528 at 20. None of these uses, however, make the subject claims patentable. In *Benson*, the claimed algorithm could have been used in research and scientific journals could have published articles about it, however, the claim was still invalid. Also, as discussed above, there are no known practical uses other than treatment for autoimmune or gastrointestinal diseases. Thus, the fact that uses for other diseases are not foreclosed, if true, is of no consequence. Finally, that testing and determining metabolite levels is not preempted "so long as the doctors are not warned that doses may need to be adjusted" does not aid Plaintiff's argument because under this scenario the correlations would not be used at all. Thus, despite these supposed alternate uses, the claims "wholly pre-empt" use of the correlation such that the "prac-

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[10] The Court notes that Plaintiff's position taken here is inconsistent with the record in this case. Plaintiff has accused Defendants' researcher, Dr. Rokea el-Azhary, of infringement for conducting a study to determine whether there were different correlations for dermatologic diseases than for gastrointestinal diseases. Plaintiff's expert opined that this research amounted to infringement, and at oral argument, Plaintiff argued that its claims covered dermatologic diseases. *See* May 10, 2007 Hearing Transcript at 21:10-13.

tical effect is a patent on the [correlation] itself." *Benson*, 409 U.S. at 71-72.[11]

3. *In re Comiskey* Cannot Save Plaintiff's Claims

The recent Federal Circuit case *In re Comiskey* does not change the result. Plaintiff argues that even if the Court determines that the correlations are natural phenomena, *Comiskey* demonstrates that the inclusion of patentable subject matter (i.e. machines) in the claim makes the claims patentable under section 101. Doc. No. 593 at 1. The Court disagrees. First, this Court notes that *Comiskey* is not directly on point because the facts of that case are wholly dissimilar from the facts of the present case. Second, contrary to Plaintiff's argument, *Comiskey* does not hold that the inclusion of a machine in the claim au-

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[11] Plaintiff seeks to bolster its claims by distinguishing *Benson* and instead relying on *Chakrabarty* and *Arrhythmia*. *See* Doc. No. 528 at 21. Plaintiff argues that *Benson* is inapplicable because the claim in that case was only to the mathematical algorithm and included no limitation to any art, technology, or use. *Id.* Instead, Plaintiff points to *Chakrabarty* and *Arrhythmia* as support for its argument that the claims do not wholly preempt use of the correlations. However, this Court has already held that the claims in this case, similar to the claims in *Benson*, are only to the correlations themselves. Moreover, *Chakrabarty* is distinguishable on its facts. The claims in that case were to a new, non-naturally occurring bacterium. Conversely, in the present case the inventors did not invent a new organism, rather, they merely discovered an unpatentable natural correlation. *Arrhythmia* is also inapposite. In that case the court applied the so-called *Freeman-Walter-Abele* test, which the Federal Circuit has since held "has little, if any, applicably to determining the presence of statutory subject matter." *See Arrhythmia*, 958 F.2d at 1059-60; *State Street*, 149 F.3d at 1374.

tomatically makes the claims patentable. Third, if the Court were to apply the *Comiskey* analysis to the present case, the claims of the patents-in-suit are still unpatentable under section 101.

Comiskey involved an application for a business method patent on a system of mandatory arbitration of disputes involving legal documents such as wills and contracts. 499 F.3d at 1368. Some of the claims contained multiple mental steps, but did not require the use of any technology, while other claims required the use of a computer or other device to perform the steps of the method. *Id.* at 1369, 1379. Indeed, the later claims recited the use of technology in the claims themselves: "wherein access to the mandatory arbitration is established through the Internet, intranet, World Wide Web, software applications, telephone, television, cable, video [or radio], magnetic, electronic communication, or other communication means." *Id.* at 1379. The Federal Circuit reviewed the claims for compliance with section 101, and held that the claims which did not require the use of a computer amounted to abstract mental processes that could not be patented under section 101. *Id.* at 1381. At the same time, however, the court held that the claims which required the use of a computer or other device claimed patentable subject matter under section 101 (though the claims were remanded so the Patent Office could determine whether the use of the technology would have been non-obvious under 35 U.S.C. § 103). *Id.* In reaching this decision, the court explained that "while the mere use of the machine to collect data necessary for application of the mental process may not make the claim patentable subject matter, these claims in combining the use of machines with a mental

process, claim patentable subject matter." *Id.* at 1380 (citations omitted). Thus, the distinction between the patentable claims and the unpatentable claims was whether the claims were "tied to a particular apparatus." *Id.* at 1379.

Relying on *Comiskey*, Plaintiff argues that the patents-in-suit meet the requirements of section 101 because the claims "involve specific machines." Doc. No. 593 at 2. According to Plaintiff, the asserted claims of the patents-in-suit "inherently require" the use of "specific machines" to detect the levels of metabolites. Doc. No. 588 at 14. "These machines include a detector, a pump and an injector." *Id.* Moreover, Plaintiff asserts, "dependent claims 6, 14, 24, 30 and 53 of the '623 Patent expressly require the use of a machine capable of performing high pressure liquid chromatography (HPLC)." *Id.* Thus, according to Plaintiff, the claims are patentable.

However, even assuming *arguendo* that *Comiskey* is applicable, Plaintiff's reading of the case is too broad. Plaintiff would have the Court find that under *Comiskey*, any "involvement" of a machine or composition of matter in a method claim is enough to render the claims patentable under section 101. *See id.* at 1. However, prior case law suggests that this is not the rule. Instead, the Supreme Court has previously held claims unpatentable under section 101 even though they "involve" a machine or composition of matter. In *Flook* the Supreme Court held claims invalid under section 101 even though they involved the catalytic chemical conversion of hydrocarbons, which are compositions of matter. 437 U.S. at 596. Similarly, in *Benson* the patentees sought to claim "a method of programming a general-purpose digital

computer to convert signals from binary-coded decimal form into pure binary form," and despite the clear involvement of a computer, the Court held the claims unpatentable under section 101. 409 U.S. at 65. The Federal Circuit has done the same. In *Grams* the court held claims unpatentable under section 101 even though one step of the claim required the use of a machine. 888 F.2d at 836. In that case the claims covered a "method of diagnosing an abnormal condition in an individual." *Id.* The first, and only physical, step in the claim was "performing clinical tests on individuals to obtain data." *Id.* at 840. The clinical tests were "produced by a standard chemical analyzer that measures the levels of the chemical biological components," i.e. a machine. Nonetheless, the Federal Circuit held the claims unpatentable under section 101. The difference between those cases and *Comiskey* is that in *Flook*, *Benson* and *Gram* the use of the machine or composition of matter was merely incidental, while in *Comiskey* the machine was "tied to" the operation of the claim and in fact recited in the claim. Thus, the better reading of *Comiskey* is that claims which are "tied to a particular apparatus" may be invalid, while claims that involve machines in a merely incidental fashion are not foreclosed.

Applying *Comiskey* to the present case, the patents-in-suit would be invalid *if* the claims were "tied to a particular apparatus." However, this is not the case. Rather, the machines identified by Plaintiff are merely incidental to the claims just as in *Flook*, *Benson* and *Grams*. The present case is most similar to *Grams* as the "determining" step in the present case is analogous to the "performing" step in *Grams*. In both instances, the mere involvement of a machine in a data-gathering step cannot render the claim statu-

tory. *See Grams*, 888 F.2d at 840. Moreover, the patents-in-suit are easily distinguishable from the claims at issue in *Comiskey*. In *Comiskey*, the use of technology was explicitly recited in the claims. *See id.* at 1379. However, the patents-in-suit do not even mention any machines, thus it would be disproportionate to conclude that the claims are "tied to a particular apparatus." It follows that even applying *Comiskey*, the claims of the patents-in-suit are invalid under section 101.

4. There Are No Genuine Issues of Material Fact Precluding Summary Judgment

In its final effort, Plaintiff argues that there are four underlying factual issues precluding summary judgment in Defendants' favor: (1) whether the claims at issue claim a "natural phenomenon"; (2) whether the claims at issue transform an article into a different state or thing; (3) whether the claims at issue produce a useful, concrete, and tangible result; and (4) whether the claims at issue "wholly preempt" all uses of the inventors' correlation. Doc. No. 528 at 27. However, these issues do not represent factual disputes, and instead concern interpretation of the claims and the proper application of section 101 to the facts of this case. These are clearly questions of law, and are thus appropriate for summary judgment. *See AT&T Corp.*, 172 F.3d at 1355 (explaining that whether a patent claim is invalid under section 101 is a question of law appropriate for summary judgment).

5. Conclusion

Based on the foregoing, this Court finds that there is no genuine issue of material fact to be resolved as to whether the patents-in-suit are directed to statutory subject matter in compliance with 35 U.S.C. § 101. This Court finds by clear and convincing evidence that the patents-in-suit recite a natural phenomenon – the correlations between thiopurine drug metabolite levels and therapeutic efficacy and/or toxicity – and the claims "wholly pre-empt" use of said correlations. Therefore, the claims are invalid under section 101.

CONCLUSION AND ORDER

Accordingly, IT IS HEREBY ORDERED that Defendants' motion for summary judgment on patent invalidity pursuant to 35 U.S.C. § 101 is **GRANTED**.

IT IS FURTHER ORDERED that:

1. Plaintiff's motion for summary judgment of no patent exhaustion is **DENIED as moot.**
2. Plaintiff's motion for summary judgment for declaratory infringement of patent nos. 6,355,623 and 6,680,302 is **DENIED as moot.**
3. Plaintiff's motion to strike the declaration of Dr. Bruce Bostrom is **DENIED as moot.**

DATED: March 28, 2008

/s/
JOHN A. HOUSTON
United States District Judge

APPENDIX E

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

Civil No. 04cv1200 JAH (RBB)

PROMETHEUS LABORATORIES, INC.,
Plaintiff,

v.

MAYO COLLABORATIVE SERVICES dba MAYO MEDICAL LABORATORIES AND MAYO CLINIC ROCHESTER,
Defendants

AND RELATED COUNTERCLAIM.

ORDER DENYING DEFENDANT'S MOTION FOR SUMMARY JUDGMENT [DOC #14] AND GRANTING PLAINTIFF'S CROSS-MOTION FOR SUMMARY JUDGMENT [DOC #135]

INTRODUCTION

This matter is now before the Court on the parties' cross-motions for summary judgment. The parties' motions have been fully briefed and oral argument was entertained. After a careful consideration of the pleadings and relevant exhibits submitted by the parties, the oral argument presented at the hearing, and for the reasons set forth below, this Court DENIES defendant's motion for summary judgment and GRANTS plaintiff's cross-motion.

BACKGROUND

1. Factual Background

Plaintiff is the exclusive licensee of two patents: U.S. Patent Nos. 6,355,623 ("the '623 patent") and 6,680,302 ("the '302 patent"). The patents-in-suit involve technology used in blood tests for the treatment of patients with various inflammatory bowel diseases and other autoimmune diseases. The patented technology provides the means for measuring the level of certain metabolites[1] in the blood in patients that were treated with thiopurine drugs, including the anti-Crohn's disease drug, azathioprine ("AZA"). The test using the patented technology ("the patented test") measures the level of two metabolites: 6-thioguanine ("6-TGN") and 6-methylmercaptopurine ("6-MMP"). The patented test for these metabolites measure patients' 6-TGN and 6-MMP, indicating that drug usage should be reduced at levels "greater than about 400" and "greater than about 7000," respectively, in order to avoid toxic side effects.

Defendant Mayo Collaborative Services dba Mayo Medical Laboratories ("defendant") developed a test ("the accused test") to measure the same metabolites but using different levels, 450 6-TGN and 5700 6-MMP. In June 2004, defendant announced it will begin to use its accused test, offering it for sale to potential purchasers.[2] The instant lawsuit followed.

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[1] Metabolites are compounds formed when the body breaks down a drug.

[2] Defendant explained, during oral argument, that it rescinded its announcement after the inception of this lawsuit and the ac-

2. Procedural History

Plaintiff filed its patent infringement complaint on June 15, 2004. Defendant filed an answer to the complaint, along with a counterclaim, on October 6, 2004. Plaintiff filed an answer to the counterclaim on October 29, 2004.

Defendant filed its motion for summary judgment on January 27, 2005, with the hearing initially scheduled for March 27, 2005. Plaintiff, on February 17, 2005, filed an *ex parte* application seeking to continue the hearing date for defendant's summary judgment motion in order to allow for a *Markman* hearing to be conducted. Plaintiff's *ex parte* application was subsequently denied but the Court rescheduled the summary judgment motion hearing to April 7, 2005. The parties then stipulated to continue the hearing until April 21, 2005. Plaintiff filed its opposition to defendant's summary judgment motion on March 24, 2005, under seal. Defendant's reply brief was filed on March 24, 2005.

On April 12, 2005, plaintiff filed objections to defendant's facts and evidence submitted in support of its motion for summary judgment. On April 21, 2005, defendant, in response, filed a motion to strike plaintiff's objections as untimely filed.[3] On April 15, 2005,

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cused test has not been implemented as of the date of the hearing.

[3] Plaintiff filed its objections to the facts and evidence presented by defendant in support of its motion for summary judgment well after the deadline set for filing its opposition, in which such objections should have been presented. *See* CivLR 7.1 (e.2). Plaintiff does not present any reason to excuse the untimely filing. Accordingly, defendant's motion to strike plaintiff's objections to defendant's facts and evidence [doc. #73] is GRANTED.

plaintiff submitted an *ex parte* application for leave to file a sur-reply in further opposition to defendant's motion for summary judgment. Defendant opposed the *ex parte* request and plaintiff filed a reply to defendant's opposition to the request. The Court subsequently, on its own motion, rescheduled the April 21, 2005 motion hearing to June 16, 2005. Then, on May 12, 2005, the Court, again on its own motion, rescheduled the hearing until August 4, 2005.

On June 30, 2005, Magistrate Judge Ruben B. Brooks conducted a case management conference, during which the following orders were entered, among others:[4]

1. The hearing date on defendant's motion for summary judgment was rescheduled to September 15, 2005.
2. Plaintiff's cross-motion was set for hearing the same date and directed to be filed by August 4, 2005.
3. Plaintiff's request to file a supplemental opposition defendant's motion was granted and directed to be filed by August 4, 2005.
4. Defendant was granted the opportunity to file a supplemental reply to plaintiff's supplemental opposition. Defendant's supplemental reply and opposition to

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[4] Judge Brooks also vacated the hearing date set for defendant's motion for leave to file an amended answer and counterclaim, taking that motion, along with plaintiff's motion seeking leave to file an amended complaint adding Mayo Clinic Rochester as a defendant, under submission without oral argument. The motions are currently pending before this Court.

plaintiff's summary judgment motion was due by August 15, 2005.

5. Plaintiff's reply in support of its cross-motion was due by August 25, 2005.

6. Plaintiff's *ex parte* application to file a sur-reply was denied as moot.

Plaintiff filed its cross-motion, under seal, on August 9, 2005. On August 11, 2005, the Court, on its own motion, rescheduled the motion hearing on the cross-motions for summary judgment to September 29, 2005. Defendant filed an opposition to plaintiff's motion and a supplemental reply brief in support of its motion on August 19, 2005. Plaintiff filed its reply brief on September 2, 2005.

This Court entertained oral argument by the parties on September 29, 2005. Prior to commencement of oral argument, the Court unsealed all documents sealed in conjunction with these motions. At the conclusion of the hearing the Court directed the parties to submit rebuttal and supplemental briefing. Defendant filed its rebuttal brief on October 3, 2005. Plaintiff's supplemental brief was filed on October 4, 2005 and its sur-rebuttal brief was filed on October 7, 2005. Defendant's response to plaintiff's supplemental brief was also filed on October 7, 2005. On October 14, 2005, defendant submitted an *ex parte* application seeking leave to file a supplemental response to plaintiff's Rule 56(f) supplemental brief. Plaintiff, on October 27, 2005, filed a rebuttal brief to defendant's supplemental response.

DISCUSSION

Defendant moves for summary judgment, contending there is no genuine issue of material fact to

be resolved in this case and seeking a declaration of non-infringement of the patents-in-suit. Defendant contends that, when the patents-in-suit are properly construed, the accused test does not infringe plaintiff's patents, either literally or through the doctrine of equivalents. Plaintiff cross-moves for summary judgment, seeking a judicial declaration that defendant's accused test literally infringes Claim 7 of the '623 patent.

1. Summary Judgment Legal Standard

A moving party who demonstrates that the "pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact" may be entitled to summary judgment as a matter of law under Fed. R. Civ. P. 56(c). The nonmoving party can defeat summary judgment by demonstrating that a material issue of fact exists. *See Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986). A fact is material when it is outcome determinative. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986).

When ruling on a summary judgment motion, the Court must examine all the evidence in the light most favorable to the non-moving party. *Morgan v. United States*, 709 F.2d 580, 584 (9th Cir. 1983). The Court cannot engage in credibility determinations, weighing of evidence, or drawing of legitimate inferences from the facts; these functions are for the jury. *Anderson*, 477 U.S. at 255.

A material fact is one that is relevant to an element of a claim or defense and the existence of which might affect the outcome of the suit. The materiality of a fact is thus determined by the substantive law

governing the claim or defense. Disputes over irrelevant or unnecessary facts will not preclude a grant of summary judgment. *T.W. Electrical Service, Inc. v. Pacific Electrical Contractors Ass'n*, 809 F.2d 626, 630 (9th Cir. 1987) (citing *Anderson*, 477 U.S. at 248).

Entry of summary judgment is appropriate "against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex*, 477 U.S. at 322. Without specific facts to support the conclusion, a bald assertion of the "ultimate fact" is insufficient. *See Schneider v. TRW, Inc.*, 938 F.2d 986, 990-91 (9th Cir. 1991).

Cross-motions for summary judgment do not necessarily permit the judge to render judgment in favor of one side or the other. *Starsky v. Williams*, 512 F.2d 109, 112 (9th Cir. 1975). The Court must consider each motion separately "on its own merits" to determine whether any genuine issue of material fact exists. *Fair Housing Council of Riverside County, Inc. v. Riverside Two*, 249 F.3d 1132, 1136 (9th Cir. 2001); *Starsky*, 512 F.2d at 112. When evaluating cross-motions for summary judgment, the Court must analyze whether the record demonstrates the existence of genuine issues of material fact, both in cases where both parties assert that no material factual issues exist, as well as where the parties dispute the facts. *See Fair Housing Council of Riverside County*, 249 F.3d at 1136 (citing *Chevron USA, Inc. v. Cayetano*, 224 F.3d 1030, 1037 & n.5 (9th Cir. 2000)).

2. Analysis

The parties' cross-motions each seek construction of various claim terms contained in the patents-in-suit, which is required in order for the Court to properly determine the issue of infringement. *See Liquid Dynamics Corp. v. Vaughan Company*, 355 F.3d 1361, 1367 (Fed. Cir. 2004) (in patent infringement cases, the Court first determines the meaning of the asserted patent claims, and then compares the properly construed claims to the allegedly infringing device). Because a determination of infringement requires that claim terms be properly construed, claims construction will be addressed first.

A. Claims Construction

1. Legal Standard

In order to determine the meaning of the asserted patent claims, the court considers "the evidence necessary to resolve disputes about claim terms and to assign a fixed, unambiguous, legally operative meaning to the claim." *Liquid Dynamics*, 355 F.3d at 1367. The terms of a claim are given their ordinary and customary meaning, determined from the view of a person of ordinary skill in the relevant art. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). The *Phillips* court explained:

> In some cases, the ordinary meaning of claim language as understood by a person of skill in the art may be readily apparent even to lay judges, and claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words. In such circumstances, general purpose dictionaries may be helpful. In many

> cases that give rise to litigation, however, determining the ordinary and customary meaning of the claim requires examination of terms that have a particular meaning in a field of art. Because the meaning of a claim term as understood by persons of skill in the art is often not immediately apparent, and because patentees frequently use terms idiosyncratically, the court looks to 'those sources available to the public that show what a person of skill in the art would have understood disputed claim language to mean.' Those sources include 'the words of the claims themselves, the remainder of the specification, the prosecution history, and extrinsic evidence concerning relevant scientific principles, the meaning of technical terms, and the state of the art.'

Id. at 1314 (internal citations omitted).

"The plain and ordinary meaning of the claim language controls, unless that meaning renders the claim unclear or is overcome by a special definition that appears in the intrinsic record with reasonable clarity and precision." *N. Telecom Ltd. V. Samsung Electronics Co.*, 215 F.3d 1281, 1295 (Fed Cir. 2000). In some cases, prosecution history can be useful to interpret claim terms, but "it cannot be used to limit the scope of a claim unless the applicant took a position before the PTO that would lead a competitor to believe that the applicant had disavowed coverage of the relevant subject matter." *Schwing GmbH v. Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1324 (Fed. Cir. 2002). Absent amendments to the patent claims, an applicant "must clearly and unambiguously express any such surrender of subject matter during prosecution." *Invitrogen Corporation v. Biocrest*

Manufacturing, 327 F.3d 1364, 1367 (Fed. Cir. 2003); *see York Products, Inc. v. Central Tractor Farm & Family Center*, 99 F.3d 1568, 1575 (Fed. Cir. 1996).

2. Analysis

At issue in these cross-motions are Claim 1 of the '302 patent and Claim 7 of the '623 patent. Claim 1 of the '302 patent states:

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and *wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.*

Bush Decl., Exh. G at 87 (emphasis added).

Claim 7 of the '623 patent states:

> 7. A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder;

> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and
>
> (c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder, *wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells or the level of 6-methyl-mercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.*

Bush Decl., Exh. A at 21 (emphasis added). In order to properly rule upon the issues presented in both motions[5] construction of the phrase "greater than about 400" as used in both patent claims is required. Plaintiff's motion also requires a proper construction of the phrase "indicates a need" as used in the '623 patent.

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[5] The parties have submitted voluminous briefs containing numerous arguments and evidence in support of their respective motions. This Court has thoroughly reviewed all arguments and relevant exhibits submitted. For the sake of brevity, this Order addresses only those arguments and evidence the Court deems relevant in determining the issues presented.

a. "Greater Than About 400"

Defendant's briefs center on construction of the "about 400" term contained in the patents-in-suit, contending that a proper construction of "about 400" would require a finding of non-infringement. *See, e.g.*, Deft's Mot. at 15-19; Reply at 5-6. Plaintiff, throughout its pleadings, notes that defendant's focus on the "about 400" language improperly ignores[6] the "greater than" language that must be considered in construing the claims at bar. *See, e.g.*, Pltff's Opp. at 15; Pltff's Suppl. Opp. at 15. This Court, after a thorough review of the patents at issue, finds that construction of both the "greater than" and "about 400" language is clearly required in order to properly construe the claims.

1. "Greater Than"

Plaintiff contends that the "greater than" language "simply means any value larger than about 400 with the understanding that the risk of toxicity increases as the 6-TG[7] level increases." Pltff's Suppl. Opp. at 15. Although defendant fails to address the "greater than" language in any of its briefs, at oral argument, defendant contends that the "greater than" language cannot be construed as covering all levels higher than "about 400" because there is no upper limit on the level of metabolites and, thus, if the "greater than" language is construed to mean

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[6] As discussed later, defendant did present arguments during the hearing in opposition to plaintiff's proposed construction of the "greater than" language.

[7] For purposes of these motions, 6-TG (6-thioguanine) and 6-TGN (6-thioguanine nucleotides) are used interchangeably. *See* Pltff's Mot. at 3, n.2.

any number higher or more than "about 400," the patents would improperly cover an indefinite number.

Plaintiff explains that no upper limit was required to be disclosed because "[l]evels of 500, 600 or more are still potentially toxic ... [for example] 6-TGN levels of '490' in adults correlate with hematologic toxicity." Pltff's Suppl. Opp. at 14 (citing Bloomfeld Decl., Exh. 1 ('623 Patent) at 32 (Example II). Plaintiff further explains that there is no reason for an upper limit since "[a]t a certain point, the level of 6-TG will be so high and so toxic that it will cause death (so it is not practically possible to have an infinite amount of 6-TG in a patient)." Pltff's Sur-Rebuttal at 3. Plaintiff admits the patents-in-suit contain no upper limit but argues that "it would be improper to read such a limitation into the claim." *Id.* (citing *Gart v. Logitech, Inc.*, 254 F.3d 1334, 1343 (Fed.Cir. 2001)). This Court's review of the patents reveals that plaintiff is correct. No upper limit is mentioned in the patents-in-suit and, thus, such limitation cannot be considered in construing the terms of the patent claims. *See Phillips*, 415 F.3d at 1312-13. Therefore, defendant's argument fails.

The patents-in-suit do not contain an express definition of "greater than." According to plaintiff, the dictionary definition of "greater than," considered along with the intrinsic evidence supports plaintiff's interpretation of the claims. Pltff's Opp. at 14. Plaintiff explains that, when the ordinary meaning of "greater than" is applied, the term means "a level of 6-TGN above 'about 400.'" Pltff's Mot. at 16. Plaintiff notes, in its reply brief, that the inventors used, as an example in the patent specification, a 490 level of 6-TGN found to correlate with hematologic toxicity in adults which "'should be monitored to avoid potential

clinical bone marrow suppression.'" Reply at 5 (quoting Bloomfield Decl., Exh. 1 at 32). Plaintiff asserts that the Federal Circuit has found construction of claims that exclude the preferred embodiment is "'rarely, if ever, correct.'" *Id.* (quoting *Interactive Gift Express, Inc. v. Compuserve, Inc.*, 256 F.3d 1323, 1343 (Fed. Cir. 2001)). Plaintiff explains that "greater than" as used in the patents means "[a]ny level that is above [about 400]" and "[a]ny level which is lower than [about 400] is not a level which is greater than [about 400]." Pltff's Sur-Rebuttal at 2. Defendant does not dispute plaintiff's construction nor present its own proposed construction of the term.[8]

This Court finds that plaintiff's construction of "greater than" defined as "any level that is above about 400" is a proper construction of the term based on its "ordinary and customary meaning, determined from the view of a person of ordinary skill in the relevant art." *Phillips*, 415 F.3d at 1312-13. Therefore,

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[8] Plaintiff, however, construes defendant's oral argument as presenting a definition of "greater than" which "requires (1) "a comparison of the 6-TG level to 'about 400' and (2) a finding that the 6-TG level is greater than 'about 400.'" Pltff's Sur-Rebuttal at 7. Although plaintiff's construction of defendant's argument generously provides defendant with a definition of the term, this Court's does not so construe defendant's arguments, written or oral. This Court does not believe defendant intended to present a definition of "greater than" by adding requirements to the term. Even if defendant had so intended, this Court deems it improper to construe a term by adding additional requirements to alter its plain meaning. *See Phillips*, 415 F.3d at 1312-13. Because defendant presents no other possible construction of "greater than," this Court finds defendant does not present its own construction of "greater than" and addresses only plaintiff's proposed construction.

this Court construes "greater than" to mean any level that is above "about 400."

2. "About 400"

Both parties appear to agree that the patents-in-suit contain no express definition of the word "about" but differ on whether the Court should consult extrinsic evidence to determine its meaning. Defendant urges the Court to construe the word "about" without consulting extrinsic sources. Plaintiff disagrees, contending that, because the word is not expressly defined in the patent, consulting extrinsic evidence is necessary to properly define the word. The *Phillips* court, discussing the use of extrinsic evidence in claims construction, instructs that:

> ... extrinsic evidence may be useful to the court, but is unlikely to result in a reliable interpretation of patent claim scope unless considered in the context of the intrinsic evidence. Nonetheless, because extrinsic evidence can help educate the court regarding the field of the invention and can help the court determine what a person of ordinary skill in the art would understand claim terms to mean, it is permissible for the district court in its sound discretion to admit and use such evidence. In exercising that discretion, and in weighing all the evidence bearing on claim construction, the court should keep in mind the flaws inherent in each type of evidence and assess that evidence accordingly.

Id., 415 F.3d at 1319.

Based on case authority defining the word "about" in various contexts, defendant contends that the

proper construction of the word "about" requires it be defined narrowly as "with some approach to exactness in quantity, number, or time[,]' 'approximately,' [or] 'reasonably close to.'" Deft's Suppl. Reply at 7 (citing *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1369-72 (Fed.Cir. 2005) ("about" means "approximately"); *Conopco, Inc. v. May Dep't Stores Co.*, 46 F.3d 1556, 1561 & n.3 (Fed.Cir. 1994) ("the term ['about'] means ... 'with some approach to exactness in quantity, number, or time,'" adopting Webster's Third New International Dictionary definition); *Cellnet Data Sys. Inc. v. Itron, Inc.*, 17 F.Supp.2d 1100, 1114 (N.D.Cal. 1998)("about" means "reasonably close to."); Bush Decl., Exh. W (Order filed by a Delaware district court, on July 26, 2005, construing "about" in patent as "approximately")).

Plaintiff, on the other hand, points to other cases that indicate the word "about" actually broadens the number, creating a range dependent upon the precision of measurement for the particular technology. Pltff's Suppl. Opp. at 7 (citing *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 127 (Fed. Cir. 1995) ("the use of the word 'about,' avoids a strict numerical boundary to the specified parameter."); *Modine Mfg. Co. v. U.S. Int'l Trade Commission*, 75 F.3d 1545, 1554 (Fed. Cir. 1996) ("about" is a "broadening usage[]" which is given a "reasonable scope" and depends on the context and precision of measurement error for the claimed technology)). Plaintiff notes that some courts have actually construed "about" to encompass much broader ranges than the cases cited by defendant. *Id.* at 7, 8 n.6 (citing, *inter alia*, *Hybritech Inc. v. Abbott Labs*, 849 F.2d 1446, 1455-56 (Fed. Cir. 1988) (using a two to three fold error in measuring antibodies); *Schreiber Foods, Inc. v. Saputo*

Cheese USA Inc., 83 F.Supp.2d 942 (N.D. Ill. 2000) (construing "about 2 minutes to about 4 minutes" as encompassing 30 seconds to ten minutes and "about 190 degrees to about 205" as including 150 to 300 degrees)).

Although defendant argues, during oral argument, that no specific range of numbers should be used in defining "about 400," plaintiff contends the proper construction of "about 400" is a range of "400 +/-15-20%," based on extrinsic sources. *See* Pltff's Suppl. Opp. at 8-13. Plaintiff points to various sources of extrinsic evidence, including the Food and Drug Administration ("FDA") guidelines, scientific articles, defendant's documents, expert testimony, and the inventors' testimony, in support of the broader interpretation. *See id.* at 10-13. Plaintiff explains the FDA guidelines are useful in determining what a person of ordinary skill in the art would understand the word "about" means, as used in the patents-in-suit. *Id.* Plaintiff claims that the Federal Circuit "*expressly approved*" the use of FDA guidelines in claims construction and decision in *Phillips* did not alter that approval. *Id.* (emphasis in original) (citing *Key Pharm. v. Hercon Labs Corp.*, 161 F.3d 709, 718 (Fed. Cir. 1998) ("it is quite sensible to look to the FDA" guidelines on measurements in order to properly construe a claim term.)). Plaintiff points out the FDA guidelines provide a standard for precision and accuracy in blood testing of +/- 15% or, at the lowest level of detection, 20%. *Id.* at 4 & n.4. Plaintiff notes that the appropriate variation for the patented test is 15% because the lowest level of detection, considered the most imprecise level warranting a 20% variation, is not applicable here. *Id.* Thus, plaintiff contends a person of ordinary skill in the art would

understand "about 400" to mean "400 +/-15%." *Id.* at 4-5.

In its rebuttal brief, defendant urges the Court to discount the FDA guidelines' usefulness here[9] because "[t]hey generally establish outer limits for acceptability for the measurement of metabolite levels under a wide variety of circumstances, including measurements in animals" and "say nothing about the actual precision of tests measuring 6-TG or 6-MMP." Deft's Rebuttal at 5-6. Defendant suggests, instead, that the Court look to "the only record evidence regarding the actual precision of tests measuring" these metabolites – defendant's accused test, which lists a precision of 1.5 - 3.8%. *Id.* at 6. Plaintiff, in response, contends defendant's suggestion to use its own test's precision rate is "absurd" because the accused test was developed well after the patents-in-suit were filed. Pltff's Sur-Rebuttal at 4, n.3. Plaintiff argues that to do so would be clear error. *Id.* (citing *SRI International v. Matsuchita Elec. Corp. of America*, 775 F.2d 1107, 1118 (Fed.Cir. 1985)).

This Court finds defendant's proposed definitions of "about" to mean "with some approach to exactness in quantity, number, or time," "approximately" and "reasonably close to," although extracted from case authority, are too vague to be useful in the context of

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[9] Defendant does not appear to dispute that the 2001 guidelines are the applicable guidelines for the patents-in-suit. This Court notes that the FDA implemented the guidelines in 2001 based on the deliberations of two prior workshops held in 1990 and 2000. *See* Morgan Decl., Exh. 6 at 624. This Court's independent research reveals no earlier edition of FDA guidelines existed at the time the 2001 guidelines were issued. Thus, this Court finds the 2001 FDA guidelines are properly applicable to the instant patents.

the metabolite measurements at issue here. These definitions fail to impart a specific numerical range a person of ordinary skill in the art would understand equates to a metabolite level of "about 400." In fact, defendant admits, during oral argument, that its construction does not does not delineate a specific numerical range, but contends the Court is not required to do so in order to properly construe the claim term. This Court is unconvinced that a person of ordinary skill in the art would define "about 400" without determining a specific numerical range encompassing the amount. Accordingly, this Court deems it appropriate to resort to extrinsic evidence to determine the specific numerical range imparted by the term "about 400" as a person of ordinary skill in the art would understand it.

As noted previously, defendant presents no extrinsic evidence to aid in the Court's claims construction. Plaintiff, on the other hand, presents various sources of extrinsic evidence, including declarations of expert witnesses and the inventors of the patents-in-suit, as well as a variety of documentary evidence. This Court is mindful that the declarations of expert witnesses and the inventors are, for the most part, to be viewed cautiously because such evidence is "generated at the time of and for the purpose of litigation and thus can suffer from bias." *Phillips*, 415 F.3d at 1318. However, this Court finds that consideration of the declarations submitted by plaintiff are not necessary to properly construe the claim term at issue. Thus, the declarations of expert witnesses and the patent inventors will not be considered.

Plaintiff relies heavily upon the FDA guidelines to support its proposed construction. This Court is unpersuaded by defendant's characterization of the

FDA guidelines as unreliable because they establish general guidelines used in a variety of areas and are, therefore, not specific guidelines for measuring the metabolites involved in this suit. Defendant's suggestion to use the accused test's stated accuracy rate instead is, in this Court's view, inappropriate because the test was developed after the '623 patent was filed and the FDA guidelines were issued.[10]

As plaintiff notes, the Federal Circuit agrees the FDA guidelines may be useful in claims construction. *See Key Pharm.*, 161 F.3d at 718. This Court finds the FDA guidelines useful here. This Court deems the FDA guidelines reliable, in that they can be considered in the same genre as dictionaries and treatises since they do not suffer from the bias expert witness testimony presents. The *Phillips* court expressly approved the use of dictionaries and technical treatises in claims construction as long as "'the dictionary definition does not contradict any definition found in or ascertained by a reading of the patent documents.'" *Id.*, 415 F.3d at 1322-23 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1584 n.6 (Fed.Cir. 1996)).

In that vein, defendant contends that the patent specification contains references to various other levels mentioned in prior art which were not claimed in the patents-in-suit.[11] According to defendant, the

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[10] This Court notes that the only evidence presented by defendant of the claimed accuracy rate of its accused test comes from the deposition testimony of a physician (apparently an expert witness), which is the type of evidence the *Phillips* court found to be extremely unreliable. *See Phillips*, 415 F.3d at 1318.

[11] Defendant also contends plaintiff's proposed construction would render the patents invalid for indefiniteness because the

patent specification of both patents-in-suit state that, in addition to an "about 400" toxicity level for 6-TGN, levels "'also can be about 350 pmol[12] per $8x10^8$ RBC, 370 pmol per $8x10^8$ RBC, 390 pmol $8x10^8$ RBC, 425 pmol per $8x\ 10^8$ RBC; or 450 $8x\ 10^8$ RBCs.'" Deft's Mot. at 20 (quoting Bush Decl., Exh. A at 12 & Exh. G at 13). Thus, defendant argues those claimed levels are dedicated to the public[13] and cannot now be

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construction "does not provide the public with adequate notice of what the range of 'about 400' covers." Deft's Suppl. Reply at 10. Claims are indefinite if they do not "adequately notif[y] the public of the patentee's right to exclude." *Honeywell Intern., Inc. v. I.T.C.*, 341 F.3d 1332, 1338 (Fed. Cir. 2003). However, as plaintiff correctly notes, it is improper to consider patent validity in determining claim construction unless the patent claims are found to be ambiguous, which is not the case here. *See* Pltff's Reply at 8-9 (citing *Phillips*, 415 F.3d at 1327).

[12] The letters "pmol" is an abbreviation for the word picomole, which is a unit of measurement for metabolites used in medical tests. In the Sanborn patent, levels of 6-TGN and 6-MMP are expressed in terms of how many picomoles are in every 10^8 red blood cells while the patents-in-suit levels are expressed in terms of how many picomoles are in every $8x10^8$ red blood cells. Defendant claims that Dr. Sandborn's use of 10^8 (or 100,000,000) instead of $8x10^8$ (or 800,000,000) "is clearly a typographical error" in the earlier patent. *See* Deft's Mot. at 4-5. However, plaintiff notes that what defendant "believes" is "irrelevant" because Dr. Sandborn's patent uses 10^8 red blood cells and no attempts to correct what defendant believes is a mistake have been made. Pltff's Opp. at 14, n.4. This Court finds it inappropriate to interpret or construct the terms contained in the Sanborn patent to correct alleged errors because such interpretation is immaterial to the resolution of the issues here. Thus, this Court declines to resolve the issue.

[13] Plaintiff disputes defendant's use of the doctrine of dedication to the public in the context of claims construction because the doctrine has only been applied as a defense to liability for infringement based on the doctrine of equivalents. *See* Pltff's Sur-Rebuttal at 13. The argument presented by defendant is that plaintiff disclosed the claimed levels in the patent specifi-

claimed by the patentees. Defendant contends the patent applicants presented arguments to the patent office indicating the toxicity level described in prior art differed from the patents-in-suit's level recited in the patents. *Id.* at 20 (citing Bush Decl., Exh. K at 16, Exh. O at 4, Exh. N at 13). Defendant argues that "what was different, and new, about their 'invention' was the specific levels of 6-TGN and 6-MMP recited in their claims." Deft's Reply at 3. Therefore, defendant contends that "about 400" cannot encompass any of the levels disclosed in the patent specification because those levels have been dedicated to the public.

In response, plaintiff contends that "the phrase 'about 400' denotes the lower limit of a range of 6-TGN values beginning at 400." Pltff's Opp. at 15. Plaintiff claims that the portions of the specification defendant refers to are actually consistent with plaintiff's construction "because the specification explicitly states that a 'predetermined toxic level' is not an exact number but rather a range." Pltff's Reply at 6. Thus, according to plaintiff, the ranges mentioned in the specification are different ranges than "about 400" but overlap. *Id.* at 9-10.

As to defendant's argument that plaintiff disavowed the disclosed levels during prosecution, plaintiff points out that statements made during prosecution will not disclaim the scope of the claim absent a clear and unequivocal disavowal by the ap-

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cation but did not claim them in the patent, thereby rendering the disclosed levels available for public use. Defendant's public use argument is similar, but not identical, to the doctrine of dedication to the public referred to by plaintiff and is, in this Court's view, a valid argument in determining claims construction.

plicant, which did not happen here. *Id.* at 7 (citing *IMS Tech., Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, 1433-34 (Fed. Cir. 2000); *Aquatex Indus., Inc. v. Techniche Solutions*, 419 F.3d 1374, 1382-83 (Fed. Cir. Aug. 19, 2005)). Plaintiff observes that the Federal Circuit warned a patent's prosecution history may not be useful in claim construction because "'it represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation.'" *Id.* (quoting *Phillips*, 415 F.3d at 1317). Plaintiff contends that, in this case, no "clear and unequivocal" disavowal of the disclosed levels was expressed during prosecution of the patents and, thus, no disclaimer of that level can now be found. *Id.* at 7-8.

This Court's review of the record reveals plaintiff did not clearly and unequivocally disavow the disclosed levels in the patents. Although the patent applicants disclosed various levels during prosecution, the levels were disclosed by stating that the levels "can also be about 350 pmol ..." *See* Bush Decl., Exh. A at 12. This Court is not persuaded that prefacing disclosures with "can also be" may be considered a clear and unequivocal disavowal of the subject matter. This Court has found no indication in the intrinsic record that the disclosed levels were clearly and unequivocally disavowed by the patent applicants. Therefore, the patentee's disclosure and failure to claim the levels does not operate as a disclaimer of the use of those levels. *IMS Tech*, 206 F.3d at 1433-34; *Aquatex*, 419 F.3d at 1382-83. This Court thus finds the range of "about 400" may properly encompass the disclosed levels.

A careful review of the intrinsic record has discovered no other language that might contradict

plaintiff's proposed definition of "about." Therefore, based on the reliable extrinsic evidence provided by plaintiff, this Court finds that the term "about" means "+/- 15%" based on its "ordinary and customary meaning, determined from the view of a person of ordinary skill in the relevant art." *Phillips*, 415 F.3d at 1312-13. Accordingly, "about 400" is construed as 400 +/- 15% encompassing a numerical range of 340 to 460.

b. "Indicates a Need"

Plaintiff also contends that the term "indicates a need" as used in the patents-in-suit should be properly construed in order to determine infringement in this case. According to plaintiff, "indicates a need" is "a marker or warning that one should decrease [the] next dose of [the] drug administered" but does not require an actual decrease to occur. Pltff's Mot. at 17-18. Plaintiff claims that the patent specification, the prosecution history and extrinsic evidence supports this ordinary meaning. *Id.* at 18-21 (citing Bloomfield Decl. ¶¶ 38-47, Exh. 1 at 4, 8, 12, Exh. 3 at 284, 298-98, Exhs. 8-11, 20).

Defendant, in opposition, points out that plaintiff's proposed construction "reads the word 'need' right out of this phrase and even ignores the very dictionary definition of 'need' [plaintiff] cites in its brief." Opp. at 18. Defendant contends the intrinsic record precludes plaintiff's construction of this phrase. *Id.* According to defendant, the parties agree that "need" is defined as "a necessary duty or obligation." *Id.* (citing Morgan Decl., Exh. 16; Pltff's Mot. at 18). Defendant argues "indicates a need" can only mean "indicates a necessary duty or obligation." *Id.* Thus, defendant asserts the patent claims "require

that the metabolite levels 'indicate a necessary duty or obligation to decrease the amount of said drug subsequently administered' – i.e., an infringing test must advise doctors to lower the amount of drug if the predetermined toxic level is exceeded." *Id.* Defendant argues that plaintiff's construction, substituting "should" for "must," flies in the face of the definition of "need" presented in plaintiff's moving papers. *Id.* Defendant also points to the patent specification and the prosecution history in support of its construction. *Id.* at 19-20 (citing Bush Decl., Exh. A at 18; Exhs. L at 7, Z at 18, AA at 4). Defendant claims it is unnecessary to resort to extrinsic evidence to construe the terms. *Id.* at 22.

In reply, plaintiff disagrees with defendant's interpretation of "indicates a need," claiming defendant's proposed construction requires an actual lowering of the drug dosage if the test shows a metabolite level greater than about 400, when, in fact, the claim does not so state. Pltff's Reply at 10-11. Plaintiff points out that the inventors used the term "adjusting" in the specification but did not include the same term in the claim, even though they could have done so. *Id.*

Plaintiff contends the results of the patented test are merely one factor to be considered in adjusting dosage; the patented test does not require subsequent doses actually be lowered as defendant agues. *Id.* Plaintiff also contends that defendant's construction of "indicates a need" fails to give meaning to the word "indicate" and adds an additional requirement that doses actually be adjusted that is not part of the claim. *Id.* at 11. Plaintiff argues that such claim construction is improper. *Id.* (citing *Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1171

(Fed. Cir. 1993)(cautioning that every word in a claim must have meaning); *Interactive Gift*, 256 F.3d at 1335 (warning that limitations cannot be imported from the specification or prosecution history into the claims); *Gart v. Logitech, Inc.*, 254 F.3d 1334, 1343 (Fed. Cir. 2001)(same)). Finally, plaintiff points out that the specification and prosecution history do not indicate a deviation from the clear language of the claims that defendant's interpretation requires. *Id.* at 12-13.

This Court agrees with plaintiff. In this Court's view, "indicates a need" suggests to the doctor reviewing the test that an adjustment in dosage may be required. This Court is unpersuaded by defendant's argument that the word "need" signifies the patented test requires doctors to adjust drug dosage if the metabolite level reaches the specified level. There is nothing in the patent specification or prosecution history that leads this Court to believe that such a requirement should be found. Because "need" is prefaced by "indicates," this Court finds the phrase means that when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required, if the doctor believes that is the proper procedure. Accordingly, this Court, based on the "ordinary and customary meaning, determined from the view of a person of ordinary skill in the relevant art," construes "indicates a need" to mean "a warning that an adjustment in dosage may be required." *Phillips*, 415 F.3d at 1312-13.

3. Conclusion

Based on the foregoing, this Court construes the following terms contained in the patents-in-suit:

1. "Greater than about 400" is construed to mean "any level above 340 to 460;" and

2. "Indicates a need" is construed to mean "a warning that an adjustment in dosage may be required."

B. Infringement

1. Legal Standard

Once the claim terms are properly construed by the court, the properly construed claims "must be compared to the accused device or process." *C.R. Bard, Inc. v. United States Surgical Corp.*, 388 F.3d 858, 861 (Fed. Cir. 2004). To infringe a patent, a patentee must prove the accused device meets each claim limitation, either literally or under the doctrine of equivalents.[14] *Liquid Dynamics Corp. v. Vaughn Co.*, 355 F.3d 1361, 1367 (Fed. Cir. 2004).

2. Analysis

Defendant, in its summary judgment motion, seeks a declaration of non-infringement. Contrarily, plaintiff, in its cross-motion for summary judgment, contends that the accused test literally infringes

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[14] Defendant presents various arguments, in its moving papers, concerning infringement based on the doctrine of equivalents, contending that the doctrine does not apply in this case. *See* Deft's Mot. at 23-25. In opposition to defendant's motion, plaintiff argues that the doctrine of equivalents does apply. *See* Pltff's Opp. at 19. However, plaintiff's cross-motion for summary judgment, seeking a declaration of infringement, is based solely on literal infringement of Claim 7 of the '623 patent. *See* Pltff's Reply at 10. Accordingly, this Court addresses the parties' arguments concerning literal infringement only and does not address arguments concerning the doctrine of equivalents, including defendant's arguments regarding the doctrine of dedication to the public or prosecution history estoppel.

claim 7 of the '623 patent. To establish literal infringement of a patent "every limitation [or element] set forth in a claim must be found in an accused product or process." *Johnston v. IVAC Corp.*, 885 F.2d 1574, 1577 (Fed. Cir. 1989). "There can be no infringement as a matter of law if a claim limitation is totally missing from the accused device." *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1538-39 (Fed. Cir. 1991).

Defendant describes its accused test as follows:

> the accused test measures levels of 6-TGN and 6-MMP in a patient's blood, and reports these results to a treating physician. With these results, the test includes the following information:
>
> > [L]evels of 6-TGN . . . greater than 450 pmol/8x10^8 cells may be associated with increased risk of myelosuppression, liver injury, pancreatitis, and allergic reactions.
> >
> > . . .
> >
> > 6-MMP levels of >5700 pmol/8x10^8 RBC have been reported to be associated with an increased frequency of abnormal liver function tests.

Deft's Mot. at 5 (quoting Bush Decl., Exh. E at 2). Thus, the accused test informs physicians that, when metabolite levels reach 450 and above, possible complications may occur. However, the test states that "a clearly defined toxic level has not been established." Bush Decl., Exh. E at 2.

Plaintiff argues that defendant's proposed test, announced in its implementation notice dated June

9, 2004 (thus constituting an offer for sale[15]), literally infringes plaintiff's patents because the accused test:

> Meets every limitation of the method of claim 7: (1) the administration of a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; (2) determining the level of 6-thioguanine in said subject and determining the level of 6-methylmercaptopurine in said subject; and (3) wherein the level of 6-thioguanine greater than about 400 pmol $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Pltff's Mot. at 23 (citing Bloomfield Decl. ¶¶ 48-54). Plaintiff claims that defendant's accused test clearly meets the first two limitations. *See id.* at 23-24. As to the third limitation, plaintiff contends that the accused test infringes when the claim terms are properly construed as previously argued. *Id.* at 24-25.

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[15] The parties do not appear to dispute that defendant's announcement constitutes an offer for sale. An offer for sale of a patented invention by one who is not the patent owner or licensee may constitute infringement. *See* 35 U.S.C. § 271(a). Defendant argues that, because the claims in the patents-in-suit are method claims, the claims may only be infringed if the method is actually performed. Deft's Opp. at 24 (citing *Joy Technologies v. Flakt, Inc.*, 6 F.3d 770, 773 (Fed. Cir. 1993)). Defendant notes that it has only offered its test for sale and, thus, has not actually performed the test. *Id.* at 24-25. However, plaintiff, in reply, correctly points out that the statute governing patent infringement (amended after the *Joy* case, which does not involve an offer for sale) clearly states that an offer for sale creates liability for infringement. Pltff's Reply at 14, 22 (citing 35 U.S.C. § 271(a)). Therefore, defendant's argument fails.

Defendant contends, in opposition, that the accused test, if used, would not infringe the patents-in-suit for two reasons: (a) the test would not use either claimed level of "about 400" or "about 7000;"[16] and (b) the test would not "indicate a need to decrease the amount of said drug subsequently administered" to a patient. *Id.*

a. Use of "about 400"

Defendant argues, in opposition, that a proper construction of the claim terms "greater than" and "about 400" using defendant's proposed construction would render defendant's accused test not infringing plaintiff's patents. Deft's Opp. at 22. However, this Court has now adopted plaintiff's construction of the claim term "greater than," construing the term to mean "any level above" the specified level. The accused test uses a metabolite level of 450 which is clearly above the "about 400" level. This Court has also adopted plaintiff's construction of "about 400," construing the term to mean "400 +/- 15% or a range of 340 to 460." The accused test's level falls within

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[16] Defendant points out that plaintiff has failed to present evidence proving the accused test uses the level of "about 7000." Deft's Opp. at 22. Defendant contends that Claim 7 of the '623 patent requires that both levels be used "as a 'double-check' against toxicity," and defendant's accused test uses neither. *See* Deft's Rebuttal at 4-5. Plaintiff, in response, explains that Claim 7 provides for "alternative levels that serve as an indication of a need to decrease doses." Pltff's Sur-Rebuttal at 1 (emphasis omitted). This Court's review of the patent language reveals that plaintiff's interpretation is correct. Although both levels may be measured to determine whether dosage adjustment is needed, the physician is notified if either level exceeds the predetermined toxic level. Accordingly, defendant's argument that both levels must be used by the accused test in order to find infringement is without merit.

that range also. Thus, the accused test literally infringes the "greater than about 400" element of the patented test.

b. "Indicates a Need"

Defendant also contends that a proper construction of "indicates a need" would obviate any infringement because its accused test as described in the implementation notice does not inform the physician that the dosage should be changed. Deft's Opp. at 23. Instead, defendant argues that the notice informs physicians of "possible myelosuppression" which indicates the physician should consider the possibility that there is toxicity without providing a possible action to take. *Id.* (citing Bush Decl., Exh. S at 57, 61). In addition, defendant explains that the accused test would include cautionary language informing doctors to "monitor white cell count to detect myelotoxicity ... and ... TGN concentrations" and stating "that there is no defined toxic level established." *Id.* at 24 (quoting Bush Decl., Exh. S at 147; citing Bush Decl., Exh. CC). Thus, defendant contends that the 6-TGN levels are merely one factor doctors consider in treatment based on defendant's accused test's results, which does not meet the "indicates a need" prong in plaintiff's patents. *Id.*

This Court has now construed "indicates a need" to mean "a warning that an adjustment in dosage may be required." Defendant's explanation of the accused tests' procedure appears almost identical to this Court's view of the patented test's procedure. The accused test, used for patients taking AZA drugs, informs physicians that metabolites measuring above the levels stated have been known to cause certain effects, which information the doctors may

use to determine further treatment. The patented test warns physicians that, when metabolite levels reach above a certain point, an adjustment in dosage may be warranted. This Court notes that both tests are used in measuring the metabolite level in patients taking AZA drugs and inform physicians that the higher metabolite level raises the risk of toxic side effects. Defendant's test may not actually state that drug dosage should be reduced, but the fact that the accused test measures the metabolite level of patients taking AZA drugs implies that, when the risk of toxic side effects are raised, drug dosage adjustment may be one of the proper courses of action to avoid toxic side effects of the drugs. That is exactly what plaintiff's patented test warns. Therefore, this Court finds defendant's accused test literally infringes the "indicates a need" element of the patented test.

3. Conclusion

Based on the Court's construction of the claim terms at issue, and for the reasons presented, this Court finds that there is no genuine issue of material fact to be resolved as to whether defendant's accused test literally infringes plaintiff's patents. This Court finds defendant's accused test literally infringes all elements of the patents-in-suit. Because this Court has ruled in plaintiff's favor on the issue of infringement, plaintiff's Rule 56(f) motion for further discovery on that issue is moot.

CONCLUSION AND ORDER

Based on the foregoing, IT IS HEREBY ORDERED that:

1. Defendant's motion for summary judgment is **DENIED**; and

2. Plaintiff's cross-motion for summary judgment is **GRANTED**.

IT IS FURTHER ORDERED that defendant's motion to strike plaintiff's objections to defendant's facts and evidence [doc #73] and plaintiff's request for further discovery pursuant to Fed.R.Civ.P. 56(f) are **DENIED as moot.**

Dated: November 21, 2005

/s/
JOHN A. HOUSTON
United States District Judge

APPENDIX F

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

Civil No. 04cv1200 JAH (RBB)

PROMETHEUS LABORATORIES, INC.,
Plaintiff,

v.

MAYO COLLABORATIVE SERVICES dba MAYO MEDICAL LABORATORIES and MAYO CLINIC ROCHESTER,
Defendants

AND RELATED COUNTERCLAIM.

FINAL JUDGMENT

Pursuant to Federal Rule of Civil Procedure 54 and the parties' stipulation, it is hereby adjudged, ordered and decreed that:

1) The Court's March 28, 2008 Order Granting Defendants' Motion for Summary Judgment of Patent Invalidity Pursuant to 35 U.S.C. § 101 is a final judgment against Prometheus Laboratories, Inc. in this action;

2) Each and every remaining claim and counterclaim of Prometheus Laboratories Inc. is voluntarily dismissed without prejudice;

3) Each and every remaining counterclaim of defendants Mayo Collaborative Services dba Mayo Medical Laboratories, and Mayo Clinic Rochester

("Defendants") is voluntarily dismissed without prejudice;

4) Each party will bear its own fees and costs.

The clerk is directed to enter this judgment forthwith.

Dated: May 16, 2008

/s/
JOHN A. HOUSTON
UNITED STATES
DISTRICT JUDGE

OPPOSITION BRIEF

Supreme Court, U.S.
FILED
MAY 20 2011
OFFICE OF THE CLERK

No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

PETITIONERS,

v.

PROMETHEUS LABORATORIES, INC.,

RESPONDENT.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE RESPONDENT IN OPPOSITION

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QUESTION PRESENTED

Whether the Federal Circuit correctly held that concrete methods for individually calibrating the appropriate dosages of specific synthetic drugs for treatment of patients suffering from particular serious autoimmune diseases are patentable processes under 35 U.S.C. §101.

RULE 29.6 STATEMENT

The following companies own 10% or more of Prometheus Laboratories Inc.'s stock: Apax Partners, Patricof & Co. Ventures, Inc., DLJ Banking Partners, Wachovia Capital Partners, the Sprout Group, and St. Paul Venture Capital.

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INTRODUCTION

There is no compelling reason for this Court to review the Federal Circuit's holding, which is straightforward and fact-bound. The court of appeals held merely that a specific method for improving the treatment of patients with certain diseases by better calibrating the dosage of particular synthetic drugs is a "process" under 35 U.S.C. §101, and therefore potentially patentable if it satisfies the Patent Act's other substantive requirements, such as novelty, non-obviousness, and enablement. Petitioners distort the facts and holding in an effort to manufacture a controversial legal question warranting this Court's attention. But on any fair reading, the decision below is unremarkable and perfectly consistent with this Court's precedent. This case is not about control over doctors' thoughts; it is about petitioners' for-profit laboratory attempting to produce and sell a multimillion dollar competing test, the economic value of which would derive entirely from respondent's invention.

This Court's prior grant (and dismissal) of certiorari in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) ("*LabCorp*"), provides no reason to grant certiorari here. Because the claims here describe concrete and improved methods of treating seriously ill patients and involve the administration and biochemical transformation of specified synthetic drugs, this case does not raise the issue that troubled the dissenting Justices in *LabCorp*. Moreover, this Court recently synthesized its §101 jurisprudence in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). The lower courts should have an opportunity to explore the important ramifications of that guidance

for medical diagnostic and treatment methods before this Court again intervenes.

STATEMENT OF THE CASE

A. Statutory Background

The Patent Act provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. §101. Despite petitioners' efforts throughout the litigation to import considerations relating to those *other* conditions and requirements (such as novelty and non-obviousness), the *only* issue here is whether Prometheus's claimed treatment methods describe "process[es]."

The Patent Act defines a "process" as a "process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material." *Id.* §100(b). These categories are construed broadly, as §101 is meant be given "'wide scope.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). "Congress took this permissive approach to patent eligibility to ensure that 'ingenuity should receive a liberal encouragement.'" *Id.* (quoting 5 *Writings of Thomas Jefferson* 75-76 (H. Washington ed. 1871)). The only exception is a judicially-created rule that "'laws of nature, natural phenomena, and abstract ideas'" are not themselves patentable. *Id.* at 3238 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)).

B. The Medical Problem

Immune-mediated gastrointestinal disorders, such as Crohn's disease, and other autoimmune diseases

afflict millions of individuals. CA10007.[1] Patients with these disorders often suffer from debilitating symptoms, including diarrhea, abdominal pain, arthritis, anemia, and rectal bleeding. *Id.*; CA10009-10. Physicians can treat the disorders with synthetic thiopurine drugs, such as azathiopurine (AZA) and 6-mercaptopurine (6-MP), which transform inside the body into therapeutic metabolites that suppress the patient's immune system and mitigate the symptoms. CA10007; CA10010-11; CA13073-75; CA13201.

Physicians often find it difficult, however, to determine the proper dosage for a particular patient, because individuals metabolize the drugs differently, CA10007, and it can take 3 to 6 months for the drug to demonstrate clinical benefits, CA13074. If a dosage turns out to be too high for a patient, it can result in severe, and potentially fatal, side-effects, including allergic reactions, neoplasia (cancer), hepatitis, bone marrow suppression, and pancreatitis. CA10007; CA10012. Even "minimal doses" can have toxic effects. CA13074. Historically, many physicians were thus reluctant to treat patients with these drugs, despite the potential benefits, absent a method for preventing toxic side-effects while still ensuring efficacy. CA10007.

C. Prometheus's Claimed Treatment Methods

Prometheus is a pharmaceutical and diagnostic company that develops products that help physicians treat gastrointestinal, autoimmune and inflammatory disorders. It is the sole licensee of the two patents at

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[1] Citations in the form "CA_____" refer to the Joint Appendix in the Court of Appeals.

issue. App.2a. The patents differ in certain respects, but each describes a method of improving the treatment of autoimmune diseases by permitting physicians to individually calibrate a patient's dosage without having to take a wait-and-see approach. *See* App.2a-5a; CA00028-29. These patented methods necessarily involve transformative processes, machines, and non-naturally occurring phenomena.

First, the physician administers the man-made thiopurine drugs to a patient, and the drugs are converted within the body to particular active metabolites, such as 6-thioguanine (6-TG)[2] and 6-methyl-mercaptopurine (6-MMP). CA13073-75. These metabolites do not otherwise naturally occur in the human body. CA13073.[3]

Second, the patient's metabolite levels are determined. This requires extracting a bodily sample, such as blood or oral mucosa. CA10011-12. Because "metabolite levels are not detectable in raw human tissue," all methods for measuring their concentration require "significant chemical and physical alteration of blood or human tissue" and sophisticated laboratory equipment and machines. CA13186-87; CA13503; CA10011. Some of the patents-in-suit specify the use of high pressure liquid chromatography (HPLC), which entails an intricate series of operations on the blood (including heating, centrifuging, separating, and adding various reagents), running the resulting solution

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[2] For purposes of this brief, 6-TG also refers to 6-thioguanine nucleotides (6-TGN). *See* App.3a n.1.

[3] One of the independent claims (and its associated dependent claims) assumes that the drugs have already been administered. *See* App.18a.

through a computer-controlled chromatography instrument, calculating the peak height or peak area, and feeding those figures into an equation, which finally outputs the metabolite levels. CA13186.

Third, those calculated metabolite levels are transformed into a warning to the physician about the efficacy or toxicity of the patient's dosage. A 6-TG level "greater than about 400" and a 6-MMP level "greater than about 7000" indicate that a downward adjustment in drug dosage may be required in order to avoid toxic side-effects. CA10016-18. Conversely, a 6-TG level of "less than about 230" indicates a need to increase the dosage to ensure therapeutic efficacy. *Id.* The various independent claims each recite some combination of these three pre-determined levels. *Id.*; CA10034-35.

The patents' various dependent claims further limit the method to certain disorders (such as inflammatory bowel disease), certain thiopurine drugs (such as AZA), certain methods for determining metabolite levels (such as HPLC), certain measurement units (such as red blood cells), and certain toxic side-effects (such as hepatic toxicity). *See, e.g.*, CA10016-17 ('623 Patent, dependent claims 2, 4, 5, 6, 12, 31, 32).

D. Mayo's Competing Commercial Test

Mayo Medical Laboratories and its affiliates[4] purchased and used Prometheus's patented test over 17,000 times from 1999 to 2007. App.5a-6a; CA13136. In 2004, Mayo announced that it intended to begin selling its own competing test. App.6a; CA11566.

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[4] Hereafter, Mayo Collaborative Services dba Mayo Medical Laboratories, a for-profit entity, and Mayo Clinic Rochester are referred to collectively, or individually, as "Mayo."

Mayo's test measures the same metabolites as Prometheus's test, and specifies similar metabolite levels for ensuring efficacy and avoiding toxicity. App.6a; App.111a-12a; CA11566. Mayo was poised to earn a 60% profit margin on this competing product. CA13136.

When Prometheus brought the present suit, Mayo stayed its hand. App.6a; CA10905. Mayo has noted, however, that it is anxious to "begin selling its competitive product." Appellees' Opp. to Mot. to Stay 4 (Fed. Cir. filed Aug. 11, 2008).

E. District Court Proceedings

Prompted by Mayo's announcement, Prometheus filed this patent infringement action. App.6a; CA10036-41. Mayo counterclaimed for declaratory relief of non-infringement and of patent invalidity under 35 U.S.C. §§101, 102, 103, and 112. CA10045. On cross-motions for summary judgment, the district court held that Mayo's test "literally infringes all elements of the patents-in-suit," App.115a; CA12543; *see* CA11024; CA12228, a holding that Mayo has not challenged. But the court then granted Mayo's motion to invalidate Prometheus's claims under 35 U.S.C. §101. App.83a; CA00042.

The district court only concluded that Prometheus's claims do not describe a patentable "process" by disregarding important steps. The court held that the processes' first two steps—administration of the drug and determining resulting metabolite levels—could be ignored because they are mere "conventional" or "data-gathering" steps that are not independently novel. App.62a; CA00029. Limiting its analysis to the third—"warning"—step, the court held that that step embodies only natural phenomena because it relies on

correlations that "result[] from innate metabolic activity in the human body," App.63a-71a; CA00030-35—even though the metabolites are not naturally-occurring in the human body and result from a physical transformation of the synthetic thiopurine drugs. The court thought it irrelevant whether the claimed processes "transform" matter or data, because it believed that transformation is relevant only to the patentability of "industrial" processes. App.73a; CA00036.

The court concluded that the patents "'wholly pre-empt' use of the natural phenomenon such that the 'practical effect is [an improper] patent on the [phenomenon] itself.'" App.72a; CA00035 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972)) (second alteration in original). It rejected Prometheus's argument that the patents foreclose use of the correlations only in the context of specific methods of patient treatment and do not prevent anyone from using those correlations in basic research or in the development of other treatment methods. App.75a-78a; CA00037-39.

F. Federal Circuit's First Decision And Mayo's First Cert Petition

The Federal Circuit reversed. Applying its "machine-or-transformation test," the court held that Prometheus's methods "squarely fall within the realm of patentable subject matter because they 'transform an article into a different state or thing,' and this transformation is 'central to the purpose of the claimed process.'" App.40a (citation omitted). The Federal Circuit also rejected the district court's "finding that the claims wholly preempt use of correlations between metabolite levels and efficacy or toxicity." App.47a-

48a. The court explained that the patents do not preempt all use of the correlations in the abstract, but merely describe a specific process to "utilize [the correlations] in a series of specific [treatment] steps." App.48a (citing *Diehr*, 450 U.S. at 187). The court emphasized that "the only issue" it was addressing was "whether the claims meet the requirements of §101" and that "[t]his appeal does not raise any questions about lack of novelty, obviousness, or overbreadth, since those are separate statutory requirements for patentability under §§102, 103, and 112, respectively." App.39a.

Mayo filed a petition for certiorari. While that petition was pending, this Court decided *Bilski*. The *Bilski* decision rejected two proposed "categorical" limitations on §101 patentability. First, the Court held that the machine-or-transformation test is an important tool for determining patent eligibility, but that an invention may be patent-eligible even if it does not satisfy that test. 130 S. Ct. at 3227. Second, the Court held that business method patents are not *per se* unpatentable. *Id.* at 3229. Ultimately, however, the particular business method claims at issue in *Bilski* fell short because, evaluated as a whole, they merely described the abstract idea of risk hedging and would "preempt" use of that broad concept "in all fields." *Id.* at 3229-31 (applying *Gottschalk v. Benson*, 409 U.S. 63 (1972), and *Parker v. Flook*, 437 U.S. 584 (1978), as "limited" by *Diamond v. Diehr*, 450 U.S. 175 (1981)).

In *Bilski*'s wake, this Court rejected Mayo's request for plenary review in this case, but vacated the decision below (as well as another Federal Circuit decision finding certain medical methods

*un*patentable[5]) and remanded for further consideration in light of *Bilski*. App.24a.

G. Federal Circuit's Second Decision

After supplemental briefing, the Federal Circuit again held Prometheus's methods patentable under §101. The court explained that, under *Bilski*, patent eligibility turns on whether Prometheus's claims "are drawn to a natural phenomenon, the patenting of which would entirely preempt its use as in *Benson* or *Flook*, or whether the claims are drawn only to a particular application of that phenomenon as in *Diehr*." App.12a (citing *Bilski*, 130 S. Ct. at 3230). It concluded that the claims "do not wholly preempt all uses of the recited correlations" between metabolite levels and efficacy or toxicity, but instead "involve a particular application of the natural correlations." App.15a. The court explained that "the claims do not preempt all uses of the natural processes" because they "utilize them in a series of specific steps ... comprising particular methods of treatment." *Id.* (citing *Diehr*, 450 U.S. at 187). As in *Diehr*, Prometheus's method patents "'seek only to foreclose from others the use of that [principle] in conjunction with all of the other steps in their claimed process.'" *Id.* (quoting *Diehr*, 450 U.S. at 187).

The Federal Circuit also found that the claims satisfy the "transformation prong" of the machine-or-transformation test, which, as *Bilski* explained, remains a "'useful and important clue, an investigative tool'" to patentability. App.14a-15a (quoting *Bilski*, 130 S. Ct. at 3227). The court found that the methods

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[5] *See Classen Immunotherapies, Inc. v. Biogen IDEC*, 304 F. App'x 866 (Fed. Cir. 2008), *cert. granted, vacated and remanded*, 130 S. Ct. 3541 (2010).

transform an article into a "'different state or thing'" and that this transformation is central to the purpose of the claimed process. App.14a-16a (quoting *Bilski*, 130 S. Ct. at 3227). Specifically, it determined that the method claims entail at least two transformations. First, "[w]hen administering a drug such as AZA or 6-MP, the human body *necessarily* undergoes a transformation" in response to the administration of these synthetic drugs. App.17a. Second, "[d]etermining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation." App.18a. The court explained that the determining step "clearly" involves "a transformation" because "[s]ome form of manipulation, such as the high pressure liquid chromatography ... is necessary to extract the metabolites from a bodily sample." *Id.* Indeed, "'at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue.'" *Id.* (citation omitted).

The Federal Circuit determined further that these transformations cannot be disregarded as "mere[] data-gathering" or "'insignificant extra-solution activity.'" App.18a-19a (citing *Flook*, 437 U.S. at 590). The court found that "[t]he invention's purpose to treat the human body is made clear in the specification and preambles of the asserted claims." App.17a. It explained, therefore, that "the administering step provides thiopurine drugs *for the purpose of treating disease*, and the determining step measures the drugs' metabolite levels *for the purpose of assessing the drugs' dosage during the course of treatment.*" App.20a (emphasis added). Those transformations are not peripheral or tacked-on, but "central to the claimed methods" and "'sufficiently definite to confine the

patent monopoly within rather definite bounds.'" App.18a (quoting *Benson*, 409 U.S. at 70).

Finally, the Federal Circuit explained that the inclusion of a mental step—even as the final step—does not render an otherwise patentable process unpatentable. App.21a-23a. Thus, in this case, "[a]lthough a physician is not required to make any upward or downward adjustment in dosage during the 'warning' step," the process, taken as a whole, "provide[s] useful information for possible dosage adjustments to the method of treatment using thiopurine drugs for a particular subject." App.23a.

Mayo did not seek rehearing.

REASONS FOR DENYING THE WRIT

In an effort to manufacture a legal question meriting this Court's review, Mayo attacks a straw man that bears little resemblance to the method claims actually at issue in this case. On any fair reading of the record, the decision below is an unremarkable application of longstanding principles, as reiterated in *Bilski*, to the particular facts of this case.

Prometheus's technique of combining knowledge derived from scientific discovery with useful physical activities to achieve a functional end plainly satisfies §101. The patents do not claim or preempt any purely natural phenomenon. They describe physical steps such as administering man-made drugs, drawing blood samples, and testing blood for metabolites, within an improved method for treating seriously ill patients. Each of the first two steps *standing alone* would plainly constitute a "process" that satisfies §101. Combining them, along with new knowledge, could not possibly make them less of a "process."

These patents do not claim correlations between metabolite levels and toxicity/efficacy in the abstract, but instead apply those relationships in concrete physical processes to generate useful treatment information for physicians. In that regard they are indistinguishable from the method patent this Court approved in *Diamond v. Diehr*, 450 U.S. 175 (1981), which employed an observed "natural" correlation (the Arrhenius equation) in a process for optimizing the time that rubber is left curing in a mold. *All* processes that operate in the physical world employ natural laws at some point in the process.

Rather than confronting these truths, Mayo misrepresents the scope of the patents and distorts the Federal Circuit's holding in two fundamental ways. First, Mayo wrongly asserts that the patented methods merely claim a "physician's mental determination[]" or "thought process[]," Pet.4-5, and that the methods consist of nothing more than natural phenomena and medical knowledge, Pet.17-19. Mayo (like the district court) goes astray by focusing only on the one step in the process that relies on a natural correlation or "mental step," while ignoring all the other concrete steps that confine the patent's scope. The plain language of the claims, as the court of appeals found, establishes a concrete treatment method involving specific physical steps to administer synthetic drugs, measure metabolites, and produce valuable information for use in calibrating further treatment. Mayo's attempts to ignore those undeniable physical steps—either because they were not invented by Prometheus, Pet.5, 24, or because Mayo views them as mere "data-gathering," Pet.25, 27—are contrary to the record and the law. And the idea that the administration of a

potentially toxic drug is simply "for testing, not treating," Pet.25, disregards the Federal Circuit's claim construction (and defies common sense). The Federal Circuit properly determined that the asserted claims, viewed *as a whole*, are "claims to methods of treatment" whose "purpose [is] to treat the human body." App.16a-17a.

Second, Mayo attempts to generate a conflict with this Court's precedents by misrepresenting the Federal Circuit's holding. Mayo argues that the Federal Circuit "broadly extend[ed] the 'machine or transformation' test" and "fail[ed] to give effect to the 'preemption' standard for patent-eligibility." Pet.15; *see also* Pet.24. Neither is true. The Federal Circuit faithfully applied this Court's precedent, as recounted in *Bilski*. It explained that "the claims do not preempt all uses of the natural correlations" but instead "utilize them in a series of specific steps." App.15a (applying *Diehr*, 450 U.S. at 187). And it considered the integral involvement of physical transformations as a "'useful and important clue, an investigative tool'" that in this case "leads to a clear and compelling conclusion, *viz.*, that the present claims pass muster under §101." App.14a-15a (quoting and applying *Bilski v. Kappos*, 130 S. Ct. 3218, 3227 (2010)). Mayo disagrees with the lower court's application of established law to these facts, but that is not a basis for this Court's review.

The petition's only superficial appeal is that this Court previously granted certiorari in *LabCorp*, and the patent in *LabCorp* also involved medical "correlations." But this case does not genuinely present the issue that troubled the dissenting Justices in *LabCorp*. The patent there did not involve the administration of synthetic (or, indeed, any) drugs as

part of a course of treatment for a particular disease. The *LabCorp* patent involved merely the observation of certain biological markers that exist in nature without any human agency or intervention at all, and the drawing of conclusions from that data. This Court may wish to revisit the *LabCorp* issue at some point, but it is not well presented here.

In addition, *LabCorp* preceded this Court's foundational §101 opinion in *Bilski*, which rejects "categorical limitations" on §101 in favor of case-by-case development of the law. 130 S. Ct. at 3225, 3228. The proper application of §101 in the context of medical diagnostic and treatment patents is of great importance to the public health and to multi-billion dollar industries. No doubt some of these patents will survive §101 scrutiny and others will fail. But the lower courts have barely begun to wrestle with the appropriate distinctions, particularly in light of the analysis synthesized in *Bilski*. This Court should not reach out to make wide-ranging new law on questions this important without the benefit of lower courts' development of the issues in various concrete settings.

Accordingly, the petition for a writ of certiorari should be denied.

I. MAYO'S PETITION DISTORTS THE FACTS AND RECORD BELOW

Mayo's petition is built on two fundamental distortions.

First, Mayo repeatedly asserts that the methods consist solely of a mental step. As the Federal Circuit recognized, that is not accurate. On their face and as construed by the Federal Circuit, these patents claim a concrete method of patient treatment that includes

physical steps which cannot possibly be practiced merely by thinking about scientific knowledge. Mayo believes that those physical steps should be disregarded because they are not the point of novelty of Prometheus's method claims (*i.e.*, not what Prometheus invented). *See, e.g.*, Pet.i, 3, 5 & n.2, 15, 24, 26, 30. But this Court squarely rejected that approach to §101 in *Diehr*. On any fair reading of the actual patent language, Mayo's concerns completely disappear.

Second, Mayo attempts to generate a conflict with this Court's precedents by asserting that the Federal Circuit "broadly extend[ed] the 'machine or transformation' test and fail[ed] to give effect to the 'preemption' standard for patent-eligibility." Pet.15. Both assertions are flatly incorrect. The court of appeals appropriately considered, and rejected, Mayo's preemption argument because it recognized that the patents here do not "preempt" any natural phenomena except in connection with the concrete steps specified on the face of the patents. *All* patents "preempt" specific applications of natural laws or phenomena in that sense, because nothing happens that is not governed by natural laws. And the court's consideration of the transformations that are integral to the claimed treatment method was perfectly consistent with *Bilski*'s reaffirmation of the importance of such analyses. The court's ruling was thus based on established principles, and does not conflict with any of this Court's opinions.

Once those erroneous characterizations are put aside, it is clear that the Federal Circuit's decision is well grounded in this Court's doctrine. Mayo's disagreement with the outcome provides no reason for

this Court's intervention.

A. Mayo Misrepresents the Purpose and Scope of the Patents-in-Suit

At root, Mayo simply disagrees with the Federal Circuit's claim construction, but that is no ground for this Court's review. In particular, Mayo refuses to acknowledge that these patent claims, as carefully examined by the Federal Circuit, describe concrete treatment methods involving specific steps to administer certain drugs to a patient, measure specific metabolites, and produce valuable information for use in calibrating that patient's treatment. The patents cannot be infringed by mere thought.

Mayo offers a variety of arguments for why this Court should disregard the concrete physical steps required to infringe these patents. Mayo argues, for example, that the administration and determination steps are old in the art, Pet.i, 3, 5 & n.2, 15, 24, 26, 30, and that the inventive portion of the patents targets pure mental processes, Pet.22-27; that the transformation resulting from administering the drugs is merely preparatory "data gathering," Pet.25, or a "natural" phenomenon, Pet.21, 24; and that the patents as a whole are not really about patient treatment, *e.g.*, Pet.25-26. None of these contentions has merit.

1. Mayo and its *amici* repeatedly try to import novelty analysis into §101 by arguing that the physical, transformative steps of the patents should be disregarded because those steps were previously well known in the art—and that without those steps all that remains is a mental step. *See, e.g.*, Pet.i, 3, 5 & n.2, 15, 24, 26, 30; Brief of *Amici Curiae* the American College of Medical Genetics et al. in Support of Petitioners 5, 13 ("ACMG Br."). For example, Mayo protests that

Prometheus "cobble[d] together two well-known preliminary steps" and then attached an "admittedly insufficient mental step." Pet.26. According to Mayo and its *amici*, Prometheus's claims are not patentable because what the patents "purport to add [to the art] is a recognition that *particular metabolite levels* are relevant to proper drug dosages." Pet.5; *see also* ACMG Br.5, 13.

The Federal Circuit properly recognized that "the claims are not simply to the mental steps," App.21a, and that viewed "as a whole" the processes at issue here do not consist simply of novel "correlations," App.23a. Mayo's contention that what is "novel" is improved accuracy in dosage adjustments does not make the process as a whole any less of a process.

One way to understand this point is that, as the Federal Circuit found, the initial physical steps of Prometheus's methods—administering thiopurine drugs, drawing blood, and determining metabolite levels—clearly describe "processes" that would be patent eligible under §101 and patentable by their inventor so long as the Patent Act's other requirements are met. App.21a-22a. Adding an additional step—warning the physician of a possible need to adjust dosage based on specific measurement levels—does not make the processes, individually or in the aggregate, suddenly not processes any more. App.22a ("In the instant case, the presence of the mental steps similarly does not detract from the patentability of the administering and determining steps."). Indeed, Mayo and its *amici* have effectively conceded that the patents-in-suit would satisfy §101 if Prometheus had invented either thiopurine drugs or HPLC. *See, e.g.*, Pet.5 & n.2; Pet. for Writ of

Certiorari, No. 09-490, at 18 (Oct. 22, 2009) ("Prometheus cannot take advantage of a drug that was invented by someone else ...."); ACMG Br.8 (implicitly acknowledging that "a new diagnostic test, or even a new method of diagnosing a particular disease" is patentable under §101). But whether a patent properly describes a "process" or instead an unpatentable "natural law" does not turn on who invented what.

Mayo's continued attempt to dissect these patents into old and new steps, and to ignore the latter for purposes of determining whether they describe a "process" under §101, is flatly inconsistent with longstanding precedents of this Court. In *Diehr*, this Court squarely held that process claims "must be considered as a whole," and that "[i]t is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." 450 U.S. at 188; *see also id.* at 193 n.15 ("The fact that one or more of the steps in respondents' process may not, in isolation, be novel or independently eligible for patent protection is irrelevant to the question of whether the claims as a whole recite subject matter *eligible* for patent protection under §101."). This Court reiterated these settled principles in *Bilski*. 130 S. Ct. at 3230-31. Mayo is attempting to reintroduce a conceptual error that this Court decisively banished from the law thirty years ago.

2. Mayo also argues that the initial physical steps of these patents should be ignored on the ground that they supposedly have no purpose beyond "data gathering"—they are "for testing, not treating." Pet.25. Again, the Federal Circuit rejected Mayo's assertion on the facts—correctly recognizing that the

"administering" and "determining" steps of these patents *do not* merely describe the gathering of data for an abstract equation, but rather are concrete physical steps in an ongoing method for treating desperately ill patients. "While it is true that the administering and determining steps gather useful data," that is not their sole purpose, as those two steps are integrally "part of a treatment protocol." App.19a-20a. No patient is given thiopurine drugs solely for purposes of gathering data for an equation, nor would it be ethical to do so.

Mayo also argues that the patents cannot constitute patentable treatment methods because the final step does not *require* an adjustment of dosage. Pet.22-23, 25. That argument is also misguided. The patents describe methods that produce information useful to treatment decisions. But how a doctor incorporates that information into treatment decisions may be affected by other, unrelated variables. The Federal Circuit correctly understood that "[a]lthough a physician is not required to make any upward or downward adjustment in dosage during the 'warning' step, the prior steps provide useful information for possible dosage adjustments to the method of treatment." App.23a. Thus, "[t]he addition of the mental steps to the claimed methods ... does not remove the prior two steps from that realm." App.21a.

Mayo has identified no precedent that conflicts with the Federal Circuit's conclusion that a process patent can end with a mental step. Far from being "unprecedented," Pet.22, there are literally thousands of patents on medical and other methods that "end" by providing the user with useful information. The lower courts have long recognized that such processes are

patentable. *See, e.g.*, *Arrhythmia Research Tech., Inc. v. Corazonix Corp.*, 958 F.2d 1053, 1054 (Fed. Cir. 1992) (upholding diagnostic patent producing information about patient's heart risk); *In re Abele*, 684 F.2d 902, 904, 908 & n.9 (C.C.P.A. 1982) (upholding patent on use of algorithm to improve usefulness of information provided by CAT scans, and noting that "'the fact that [the] equation is the final step is not determinative of the section 101 issue'") (citation omitted) (alteration in original); *see also Griffin v. Bertina*, 285 F.3d 1029, 1031 (Fed. Cir. 2002) (addressing patent that correlates gene mutations to risk of thrombosis); CA12939-3013 (collecting numerous such patents).

There is, moreover, no good reason why physical processes that produce useful information should, as a class, be unpatentable. The gist of Mayo's position is that a valid patent must direct the doctor to take a final, physical step or steps in response to the information generated. But (as Mayo well knows) modern medicine is far too individualized for that kind of patent drafting to be practical or desirable. Specifying exactly what a treating physician must do with useful diagnostic or treatment information would require patents to contain infinitely complex decision trees that would likely become obsolete long before the patent term expires.

Such an arbitrary and unwieldy regime would strangle rewards for innovation in biotechnology, medical diagnosis, and personalized medical care—fields in which U.S. businesses have become global leaders. *See, e.g.*, Brief of *Amicus Curiae* American Intellectual Property Law Association in Support of Appellant, No. 2008-1403, at 18-21 (Fed. Cir. Jan. 22, 2009) ("AIPLA C.A.Br."). It would also fly directly in

the teeth of *Bilski*, which denounces judicially created categorical exclusions that usurp Congress's prerogative. 130 S. Ct. at 3225-26 (stressing that §101's terms are "expansive" and that judiciary does not have "*carte blanche*" to impose new limitations); *id.* at 3227 (Kennedy, J., plurality opinion) (disavowing intent to "create uncertainty as to the patentability of ... advanced diagnostic medicine techniques"). Indeed, federal law has "explicitly contemplate[d] the existence" (*id.* at 3228) of medical method patents since at least 1996, when Congress responded to the medical community's concerns about infringement liability by immunizing certain uses of such patents rather than limiting patent eligibility. *See* 35 U.S.C. §287(c); John F. Duffy, *Rules and Standards on the Forefront of Patentability*, 51 Wm. & Mary L. Rev. 609, 634-37 (2009).

3. Although they concede that the drugs and metabolites at issue are not "naturally occurring," Mayo and its *amici* argue that Prometheus's treatment methods are not patentable because the metabolites are created by the body's "natural reaction" to these foreign substances. *See, e.g.*, Pet.24; Brief of Quest Diagnostics et al. as *Amici Curiae* in Support of Petitioners, No. 09-490, at 15 (Nov. 25, 2009) ("Quest Br.").

From the beginning of this litigation, Mayo has pretended that the patents-in-suit claim only "natural phenomena" while steadfastly ignoring the process steps that require concrete human actions. Once a drug is introduced into the human body, its metabolic effects can be predicted (and correlated) according to natural laws. But diagnostic and treatment patents that employ similar effects and correlations—such as

patents on methods of administering new drugs—are routine and uncontroversial, and have never been thought to implicate the rule against patenting natural phenomena. Mayo's contrary argument harkens back to the discredited view that "all medical or surgical methods are unpatentable subject matter merely because they involve treating the human body," which was rejected over fifty years ago in *Ex parte Scherer*, 103 U.S.P.Q. (BNA) 107, 110 (B.P.A.I. 1954).

The correlations exploited by Prometheus's patented methods embody a truth about how the physical world responds to human intervention—in the same way that the Arrhenius equation, embedded in the patent upheld in *Diehr*, expressed a truth about the physical properties of rubber when heated under pressure. Mayo's argument that these patents are suspect because they employ "naturally-occurring correlations" thus could be deployed against essentially any process, including the one in *Diehr*.

As the Federal Circuit explained, "quite literally every transformation of physical matter can be described as occurring according to natural processes and natural law." App.17a. The Federal Circuit properly recognized that any natural laws implicated in the patents-in-suit are incorporated in the context of physical processes that rely on multiple transformations. App.16a-19a.

That analysis is consistent with this Court's precedents—which have identified transformations as "a useful and important clue" to patentability of processes not involving a particular machine. *Bilski*, 130 S. Ct. at 3227; *see also Diehr*, 450 U.S. at 184; *Gottschalk v. Benson*, 409 U.S. 63, 70 (1972). *Diehr*, for example, recognized that, while "all inventions can be

reduced to underlying principles of nature," 450 U.S. at 189 n.12, there is no concern about preempting natural phenomena where methods inherently involve transformations or necessarily require machines and thus "seek only to foreclose from others the use of that [principle] in conjunction with all of the other steps in their claimed process," *id.* at 187. As the Federal Circuit determined, Prometheus's methods are patentable because they require multiple transformations and cover a "particular application" of natural processes to treat "a specific disease by administering specific drugs and measuring specific metabolites." App.15a.

The Federal Circuit's decision is fully consistent with *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, where this Court rejected an attempt to patent a combination of natural bacteria exhibiting nothing more than their natural qualities. 333 U.S. 127 (1948). There is nothing purely natural about administering synthetic drugs and deriving diagnostic information from levels of the resulting metabolites found nowhere in nature. Neither the drugs nor the patient's reaction exhibit "natural" qualities (indeed, the body's natural immune system is *suppressed* by the drugs). The Federal Circuit's decision is also consistent with *Diamond v. Chakrabarty*, where this Court held that genetically-engineered bacteria *are* patentable because they did not exist in nature. 447 U.S. 303, 310 (1980).

In sum, contrary to the assertions of Mayo and its *amici*, the decision below is consistent with this Court's precedents, as Prometheus is not attempting to patent "'basic medical knowledge,'" Pet.26 (quoting Quest Br.8-10), but instead concrete processes employing several categories of patentable subject matter.

4. Mayo protests that the patents-in-suit might randomly ensnare doctors and researchers who do nothing more than inadvertently hear or think about the identified correlations between metabolite levels and drug efficacy or toxicity. *See, e.g.*, Pet.9, 22, 29-30. That is plainly incorrect. As the Federal Circuit found, no one infringes Prometheus's treatment patents merely by thinking about correlations. App.21a-23a. Infringement occurs only after potentially toxic drugs are administered to an ill patient, blood samples are extracted, metabolite levels are measured using sophisticated scientific instruments, and a warning is provided about a possible need to adjust dosage. App.21a-22a ("[A] physician who only evaluates the result of the claimed methods, without carrying out the administering and/or determining steps that are present in all the claims, cannot infringe ...."). Those steps are not taken inadvertently, and once they are completed the benefits of the patented process have been realized—even if the patient's doctor ultimately makes a medical decision not to adjust treatment.

Mayo's protestations about unwittingly ensnared doctors are also disingenuous because Mayo admits that it wants to sell a multimillion dollar competing test to those same doctors. This case is about the infringing business plans of Mayo's for-profit diagnostic laboratory. As Mayo concedes, Prometheus does not sue doctors and did not sue Dr. el-Azhary. *See* CA10036-41, CA12595-600; CA12758-59; CA12786-87; CA12820-21. Instead, Prometheus sued the Mayo entities for infringing the patents "directly, contributorily, and by inducement of others," such as Dr. el-Azhary. CA12596.

Mayo makes much of the fact that "Dr. el-Azhary is

a dermatologist" and therefore purportedly unconcerned with the treatment protocols and metabolite ranges addressed by these patents. Pet.8-9, 22. But that is untrue. Mayo neglects to mention that the patients in Dr. el-Azhary's study were being treated for *autoimmune* dermatological conditions expressly covered in the patents. *See* CA12853-54. In particular, the patients were being treated for a "non-IBD autoimmune disease"—specifically, "an autoimmune dermatological condition, such as bullous pemphigoid and pemphigus vulgaris." CA12787; CA12820-21; CA12853. Several claims in the patents-in-suit require "administering a drug providing [6-TG] to a subject having [a] non-IBD autoimmune disease," CA10017, such as "pemphigus vulgaris," CA10014. This again highlights Mayo's persistent pattern of distorting the patents and refusing to read them as written.

B. The Federal Circuit's Fact-Specific Analysis Does Not Conflict With This Court's Preemption Standard

Mayo argues that the Federal Circuit's decision "conflicts with this Court's precedents because it broadly extends the 'machine or transformation' test" and "fails to give effect to the 'preemption' standard for patent-eligibility." Pet.15. Mayo is incorrect on both counts. The Federal Circuit's analysis is an unremarkable application of established principles to the facts of this case.

1. The Federal Circuit correctly recognized that the claims do not preempt natural processes because they only cover a "particular application" of natural processes to treat "a specific disease by administering specific drugs and measuring specific metabolites" and

"utilize [natural processes] in a series of specific steps." App.15a. Quoting *Diehr*, the Federal Circuit explained that the claims here "'do not seek to preempt the use of [a fundamental principle]'" but instead "'seek only to foreclose from others the use of that [fundamental principle] in conjunction with all of the other steps in their claimed process.'" *Id.*

The judicially-created prohibition on patents that "preempt" natural laws or phenomena is directed at patents that attempt to monopolize broad scientific principles in the abstract, like a patent on the Pythagorean Theorem, the Ideal Gas Law, or "the basic concept of hedging, or protecting against risk." *Bilski*, 130 S. Ct. at 3231. The patents here only "preempt" use of the indicated correlations in connection with the use of specific synthetic drugs and medical treatment steps—in the same way that all patented methods can be said permissibly to "preempt" specific applications of the natural principles they employ.[6] They do not preempt natural principles in any relevant (and prohibited) sense. They do not, for example, attempt to monopolize the general concept of diagnosing abnormalities, like patents the Federal Circuit has previously invalidated. *See In re Grams*, 888 F.2d 835, 836 (Fed. Cir. 1989) (process applies to "any complex system, whether it be electrical, mechanical, chemical [or] biological"); *In re Meyer*, 688

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[6] Examples include using time and temperature to cure rubber, using heat to incubate eggs, using gravity and puffs of air to separate out flour impurities, and using a blast of hot air to improve a smelting furnace. *See Diehr*, 450 U.S. at 188; *Waxham v. Smith*, 294 U.S. 20, 21 (1935); *Cochrane v. Deener*, 94 U.S. (4 Otto) 780, 784-88 (1876); *Neilson v. Harford*, 151 Eng. Rep. 1266, 1273-75 (Ex. Ct. 1841).

F.2d 789, 790 (C.C.P.A. 1982) (process applies to undefined "complex system" and indeterminate "factors" drawn from unspecified "testing"); App.20a-21a (distinguishing *Grams*). Nor do they claim a general protocol for calibrating *all* drug dosages for *all* diseases. They offer a particular means of calibrating "a method of treatment for *particular* diseases using *particular* drugs." App.23a (emphasis added).

On their face, Prometheus's patents do not even foreclose other means of treating *these particular* autoimmune diseases with *these particular* thiopurine drugs. Doctors and scientists are free to develop new ways to treat these diseases and to calibrate the drugs at issue. One can easily imagine, for example, development of a method for measuring metabolite levels that does not require analysis of a bodily sample or a *pre*-treatment diagnostic test to determine the proper dosage for each individual. Such innovations are in no way preempted by Prometheus's patents. Prometheus's claims make no attempt to cover all possible solutions to the particular problem of calibrating thiopurine drugs for treatment of specific auto-immune diseases.

Prometheus's specific, particularized treatment methods look nothing like the abstractions rejected in *Benson*, 409 U.S. at 68 (where the use could "vary from the operation of a train to verification of drivers' licenses to researching the law books for precedents"), or *Flook*, 437 U.S. at 586 (where there were a "broad range of potential uses of the method" because "[a]ll that it provides is a formula"). As the Federal Circuit held, "[t]he inventive nature of the claimed methods stems not from preemption of all use of these natural processes, but from the application of a natural

phenomenon in a series of transformative steps comprising particular methods of treatment." App.15a. And they do not even arguably preempt researchers' use of the indicated correlations to perform statistical analysis on historical patient data. For all of its complaining about "countless researchers and innovators who are paralyzed by patent monopolies like Prometheus's," Pet.19, Mayo has yet to identify any use that is preempted aside from its desire to market a competing commercial test for the exact same specific application.

2. The Federal Circuit's application of the machine-or-transformation analysis was also unremarkable—not a "Broad Extension." Pet.24. Mayo's real quibble is that it does not agree with the Federal Circuit's application of that test to the facts of this case—fundamentally, because Mayo disagrees with the Federal Circuit's reading of the patents-in-suit. But this Court has never granted certiorari in a case merely to construe the plain language of a patent.

As applied below, the machine-or-transformation test requires courts to determine not just whether the physical process steps entail transformations or machines but also whether those steps are *integral* to the purpose of the patent—*i.e.*, not merely as field of use limitations, data gathering, or other "insignificant extra-solution activity." App.19a. That analytic approach is fully consistent with, and flows from, the approach this Court took in *Diehr* and in *Bilski*. In *Diehr*, this Court held that the rubber curing processes at issue did not "seek to pre-empt the use of [a well-known mathematical] equation" because they "seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed

process"—steps that are "transformation[al]" and not mere field of use limitations or "insignificant postsolution activity." 450 U.S. at 187, 184, 191. Conversely, in *Bilski*, this Court held that "[t]he concept of hedging ... is an unpatentable abstract idea." 130 S. Ct. at 3231.

Although Mayo persists in its view that the patents-in-suit are more analogous to the abstractions rejected in *Benson* and *Flook*, *see* Pet.22-24, the Federal Circuit rightly found that Prometheus's claimed methods for optimizing the treatment of particular diseases through the improved calibration of dosages of specified drugs are most akin to the patented application of fundamental principles in *Diehr*, *see* App.15a. The Federal Circuit's opinion is in this respect a routine, fact-specific application of this Court's doctrine.

II. REVIEWING THE SCOPE OF §101 IN THE CONTEXT OF MEDICAL DIAGNOSTIC METHODS IS PREMATURE

Stripped of the mischaracterizations and manufactured conflicts, Mayo's principal argument is that certiorari is warranted here because the Court previously granted (then dismissed) certiorari in *LabCorp.* Pet.2-4, 16-21, 26, 28-29, 34; Brief of *Amici Curiae* AARP and Public Patent Foundation in Support of Petitioners 3-7 ("AARP Br."); ACMG Br.21; Quest Br.12. That argument is wrong for two reasons.

A. *LabCorp* Presented Different Issues and Provides No Basis for Granting Review

This case does not genuinely present the issues that made *LabCorp* difficult. Unlike the processes in *LabCorp*, Prometheus's processes are directed not merely at observing a naturally-occurring characteristic of the body, but at *treating* (transforming) the body by administering a safe and effective dose of a synthetic drug. The patent in *LabCorp* essentially consisted of measuring homocysteine levels and drawing conclusions from the "natural relationship between homocysteine and vitamin deficiency" that exists in any "warm-blooded animal," 548 U.S. at 129, 134 (Breyer, J., dissenting). The processes embodied in the patents-in-suit involve administering a specific synthetic drug, measuring metabolic byproducts that, absent that human intervention, would exist nowhere in nature, and considering whether the results warrant an adjustment in the patient's dosage.[7] As the American Intellectual Property Law Association explained below, there are "significant distinctions" between these patents and those in *LabCorp* because "the context of the invention in this case is the physical transformation of drugs into metabolites that can be measured to provide valuable diagnostic information" and "[t]his physical transformation is integral to the invention and establishes patent eligibility." AIPLA C.A. Br.10.

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[7] Prometheus does not argue that patentable processes must employ synthetic—as opposed to natural—drugs, only that doing so here removes any doubt as to patentability.

The Federal Circuit correctly recognized that *LabCorp* "involved different claims from the ones at issue here." App.16a n.2.[8] The Federal Circuit has previously suggested that the *LabCorp* methods might be unpatentable. *In re Bilski*, 545 F.3d 943, 965 & n.27 (Fed. Cir. 2008) (en banc). It is unnecessary for this Court to prejudge the Federal Circuit's consideration of those issues with a preemptive strike—particularly in a case that does not squarely present them.

B. The Federal Circuit Has Only Just Begun to Apply §101 To Medical Diagnostic and Treatment Methods In the Wake of *Bilski*

The application of §101 to medical diagnostic and treatment methods is in its infancy, and the district courts and the Federal Circuit should have an opportunity to explore the important distinctions in various concrete settings before this Court attempts to craft a comprehensive solution.

Just last year, in *Bilski*, this Court synthesized its precedents on §101. In addressing the business method patent in *Bilski*, however, this Court disapproved the imposition of judge-made "categorical limitations" on patentability, 130 S. Ct. at 3225, and left the further development of the law—including questions about "the patentability of software, advanced diagnostic

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[8] The Federal Circuit also rightly rejected Mayo's argument that a majority of this Court has approved of the *LabCorp* dissent's opinion of the diagnostic method claim at issue in that case. On Mayo's view, apparently, just citing (or joining an opinion that cites) an uncontroversial sentence in an opinion means that a Justice endorses every aspect of the cited opinion. *See* Pet.17-18.

medicine techniques, and inventions based on linear programming, data compression, and the manipulation of digital signals," *id.* at 3227-28 (plurality opinion)—to future case-by-case resolution. *See id.* at 3231 ("The Court ... need not define further what constitutes a patentable 'process,' beyond pointing to the [statutory] definition ... and looking to the guideposts in *Benson*, *Flook*, and *Diehr*.").

The scope of §101 is obviously of great importance in patent law, with widespread effects across many industries. This case is the Federal Circuit's first post-*Bilski* application of §101 to a medical method. The development of the law would benefit from the district courts' and Federal Circuit's consideration in the first instance of the various gradations of medical diagnostic and treatment methods on the spectrum between *Prometheus* and *LabCorp* and beyond.

Amici present a parade of "unthinkable" horribles as "*plausible* applications of the Federal Circuit's ruling" in this case. ACMG Br.13 (emphasis added). But, of course, the Federal Circuit, and ultimately this Court, will have plenty of opportunities to consider the difficult cases if and when they arise. There are cases raising a variety of issues percolating up through the lower courts.[9] The Federal Circuit was created

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[9] *See, e.g.*, *Ass'n for Molecular Pathology v. U.S. PTO*, No. 2010-1406 (Fed. Cir. argued Apr. 4, 2011) (addressing, inter alia, whether certain genetic testing methods satisfy §101); *Classen Immunotherapies, Inc. v. Biogen IDEC*, 304 F. App'x 866 (Fed. Cir. 2008) (holding certain diagnostic methods unpatentable under §101), *cert. granted, vacated and remanded*, 130 S. Ct. 3541 (2010); *see also King Pharms., Inc. v. Eon Labs, Inc.*, 593 F. Supp. 2d 501, 512-13 (E.D.N.Y. 2009) (holding certain medical methods fail

precisely for such situations—so that a specialist court could forge consistent nationwide patent law by grappling with challenging questions across a variety of factual circumstances. This Court should not reach out to make sweeping new law without the benefit of further development of these issues in concrete settings. Intervention now would be premature.

III. ADOPTION OF MAYO'S ARGUMENTS WOULD HAVE SERIOUS ADVERSE CONSEQUENCES FOR MEDICAL DIAGNOSTICS AND PERSONALIZED MEDICINE PATENTS

Mayo's policy arguments (echoed by some of its *amici*) reduce to a contention that the entire field of medical diagnosis and treatment would be better off without the patent system. *See* Pet.24-27; ACMG Br.3 ("The AMA opposes the patenting of medical procedures ...."). Mayo and its *amici* would prefer a regime in which doctors, hospitals, and for-profit medical laboratories (like Mayo's) could practice any medical method without paying patent royalties. Indeed, all of Mayo's stated concerns about "allowing patents to preempt important fields"; providing quality treatment "with an array of drugs, including those for the treatment of epilepsy, heart arrhythmias, and depression"; and "healthcare costs," Pet.30-32, would apply with equal force to the patentability of drugs or medical devices, so presumably Mayo wishes they were not patentable either. Such a regime would have certain advantages, although of course the flip-side of Mayo's vision is that pioneers and innovators in these

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under §101), *aff'd in part on other grounds*, 616 F.3d 1267 (Fed. Cir. 2010).

fields would not be incentivized by the rewards the patent system offers.

Suffice it to say that Congress has made a different judgment. In 1995, Congress considered exempting certain medical methods from patent protection, but declined to do so. H.R. 1127, 104th Cong. (1995). In 1996, Congress specifically addressed Mayo's concerns about patent liability for doctors by providing a limited immunity from patent infringement liability for the performance of certain medical procedures, but Congress pointedly *did not* exempt such procedures from patent protection generally. 35 U.S.C. §287(c); *see* Pub. L. No. 104-208, §616, 110 Stat. 3009, 3009-67 (1996). The upshot is that individual doctors generally are immune from suit, but the commercial entities that enable and induce the infringement (such as Mayo's for-profit laboratory) are not. This Court has previously found such factors significant in construing §101. *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 145 (2001) (Congress "not only failed to pass legislation indicating that it disagrees with the PTO's interpretation of §101, it has even recognized the availability of utility patents for plants.").

Mayo may be right that physicians in the course of patient care are less able to avoid patent infringement than professionals in other fields, because avoiding the patented method may be inconsistent with the physician's ethical obligations to his patient. *See* Pet.33; ACMG Br.5-6, 9-10. But that has nothing whatsoever to do with appropriate interpretation of the language of §101. *Amici* state that "[i]t is hard to imagine how the clinical diagnostic community will continue to provide quality patient care and how physicians will continue to practice medicine in an

ethical and effective manner under such a regime." ACMG Br.6. Nonsense. Mayo has no difficulty fulfilling its ethical obligations; it just has to pay inventors their appropriate reward as determined by the patent system.

Many crucial innovations in medical diagnostics and treatment involve a combination of previously-known physical steps along with mental steps or algorithms that improve the process. Rapid advances in personalized medicine will make innovations of that nature even more important than ever before, as inventors discover how existing treatments can be modified or calibrated to reflect an individual patient's particular biology. Citing "'the industry's close ties to science'" and the current "paramount national concern over health care costs and quality," Pet.32 (citation omitted), Mayo and its *amici* argue that patentability somehow will hinder the development of such personalized medicine and scientific research. *See* Pet.29-32; AARP Br.6; ACMG Br.13-16; Quest Br.15-21. But none explains why medical diagnostic and treatment methods employing innovative machines or artificial substances should be any less patentable than the machines or substances themselves. Crucial synthetic compositions and medical instruments, upon which modern medicine depends, are routinely patented with no detriment (indeed great benefit) to the provision of health care and the development of medical science.

Amici have further contended that many doctors are "trying to discern clinically relevant levels of known substances [even] without any purpose of seeking patent protection." Quest Br.20. Surely that is true, just as engineers often labor to solve difficult

problems without attempting to invoke patent protection. Congress has chosen to provide patent protection for medical diagnostic and treatment processes as it has for other technological processes. The fundamental premise of the patent system is that, in the long run, patent protection will make such beneficial inventions more available, by incentivizing inventors. As several other *amici* below recognized, "[p]atent protection is essential for continuing investment and innovation in the field of personalized medicine." AIPLA C.A. Br.21; *see also id.* at 18-21; Brief of Novartis Corp. as *Amicus Curiae* in Support of Plaintiff-Appellant and Reversal 15 (Fed. Cir. Jan. 22, 2009); Brief of *Amicus Curiae* Myriad Genetics, Inc. in Support of Appellant 10-13, 25-30 (Fed. Cir. Jan. 22, 2009); Brief of *Amici Curiae* Interested Patent Law Professors in Support of Neither Party 13-16 (Fed. Cir. Jan. 18, 2009); Corrected Brief of *Amicus Curiae* Biotechnology Industry Organization in Support of Neither Party 7-12 (Fed. Cir. Jan. 22, 2009). As these *amici* understand, advances in medical diagnostics and personalized medicine require substantial investments, and an unduly restrictive interpretation of §101 will choke these vital fields in their infancy.

CONCLUSION

The petition for a writ of certiorari should be denied.

Respectfully submitted,

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REPLY BRIEF

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In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

On Petition for A Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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Prometheus concedes (at 14, 32) that the "proper application of § 101" to medical testing and treatment is "of great importance," with "widespread effects" on "public health" and "multi-billion dollar industries." It concedes too (at 34) that if the Federal Circuit's interpretation is correct, "physicians in the course of patient care" will be "less able to avoid patent infringement than professionals in other fields" because of their "ethical obligations" to patients. Little wonder, then, that the American Medical Association and numerous other medical colleges and associations ("AMA Br."), the American Association of Retired Persons ("AARP Br."), and leading medical laboratories ("Quest Br." in No. 09-490, http://tiny.cc/osfnb) have urged this Court to grant review.

Prometheus acknowledges that its "process" consists merely of administering existing drugs and testing blood for natural metabolites—ordinary medical practice using long-established methods that Prometheus did nothing to advance—followed by consideration of a range of metabolite numbers that suggest a possible dosage change. Opp. 11-12. Prometheus believes it can stop Mayo from administering drugs, testing blood, and then using the knowledge and experience of its own researchers to conclude that Prometheus's metabolite range is *wrong* and that patients are better served by using Mayo's different range. Opp. 24, 28. Incredibly, it claims this monopoly covers *any* autoimmune disease, and asserts that infringement occurs even when a physician *rejects* dosage changes, on the theory that the physician has been warned by, *i.e.* has thought about, Prometheus's numerical ranges. Opp. 24-25. Prometheus points to just one way for physicians to escape this embargo on research and treatment—to *not use blood tests* but

instead develop entirely new ways to measure metabolite levels. Opp. 27.

The AMA describes as "profound" and "unthinkable" the practical consequences of the Federal Circuit's decision: it will "slow the development of diagnostic testing," "undermine competition to provide inexpensive and high-quality testing," and lead "to higher-priced medical treatment." AMA Br. 12-14. It was not the "intent of Congress" in Section 101 that "a process claim" should "confer power to block off whole areas of scientific development" by creating a "monopoly of knowledge." *Brenner*, 383 U.S. at 532, 534. The need for this Court's review is urgent.

1. Prometheus's contention (at 16) that this dispute centers on "claim construction" rests on empty wordplay. There is no dispute as to the nature of Prometheus's claims—as this Court recognized when it rejected precisely the same argument by vacating and remanding in response to Mayo's first certiorari petition. Prometheus's claims—the Federal Circuit, Prometheus, and Mayo agree—consist either of the three steps of administering a drug, determining metabolite levels produced by the body in biologic reaction to the drug, and then positing a metabolite range that "indicates a need" to consider changing dosage (*e.g.*, Claim 1, Pet. App. 4a), or the last two steps only (Claim 46, Pet. App. 5a). As Prometheus successfully argued in the district court, the final step does not require treatment but is satisfied when the physician or researcher is "warned" or "notified" that a dosage adjustment *may* be indicated. Pet. App. 108a-109a. The Federal Circuit reached the same conclusion. Pet. App. 23a (result is "useful information for possible dosage adjustments").

"Administering" and "determining" are not "concrete steps that confine the patent's scope." Opp. 12. They impose no limit because the final mental step—the only one to which Prometheus made any contribution—preempts all relevant uses of "naturally occurring" correlations between drugs and metabolite levels. Pet. App. 15a. Prometheus concedes as much when it says that Mayo cannot develop a better and cheaper test with different criteria relating to *any* autoimmune disease unless it invents (needlessly) an entirely new way of examining the body for metabolites. Opp. 25, 27. It does so again when it acknowledges that a physician cannot even decide *not* to use Prometheus's correlations without buying a license. Opp. 24. The broad scope of the patent is confirmed by testimony of Prometheus's expert that a physician who receives test results referring to these metabolite ranges infringes regardless whether she "crumples it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with." Pet. 22.

Prometheus downplays its attack on Mayo researcher Dr. el-Azhary with the assertion that it "does not sue doctors." Opp. 24. But it deposed Dr. el-Azhary—who was engaged in research, *not* treatment—and made a centerpiece of its argument that she infringed Prometheus's patents when she administered drugs to dermatology patients, tested their blood for metabolites, and investigated the optimal therapeutic range for dermatology patients, because Prometheus's patents monopolize the whole field. See Pet. 8-9. The chilling effect of such a sweeping patent is obvious. The AMA warns that if patents like Prometheus's stand, physicians will be entangled in "a vast thicket of exclusive rights" to "basic diagnostic information" that is "critical" to "providing

sound medical care," to "the detriment of the nation's health." AMA Br. 5-6, 20-21; see Quest Br. 15-16 (research into "more precise reference range[s]" or "other metabolites" will be "strongly deterred").

This case therefore squarely presents the issue whether a mental step that preempts a physician's judgment involving biologic correlations becomes patentable under Section 101 because it comes at the end of a "process" that consists simply of administering existing drugs and testing blood for metabolites using existing tests. *E.g.*, Opp. 21-22 (conceding question is whether Prometheus's patent on "a truth" about "the physical world" is saved by preliminary "process steps that require concrete human actions").

There is no need for Mayo "to import novelty analysis into § 101" (Opp. 16) to establish that the first two steps of Prometheus's claims are trivial and cannot save the final mental step. As in *LabCorp*, Prometheus has "simply described the natural law at issue in the abstract patent language of a 'process,'" but "[t]he question is what those steps embody." And here as in *LabCorp* that "process is no more than an instruction to read some numbers in light of medical knowledge." 548 U.S. at 137; see *Funk Bros.*, 333 U.S. at 130-132 (where "qualities are the work of nature," "packaging" that makes no difference to the way the natural principle operates is "not enough").

2. The Federal Circuit attached dispositive significance to two "transformations"—changes in the human body resulting from administration of drugs, and changes in the blood when it is tested for metabolites. Pet. App. 17a-18a, 21a-23a. The court of appeals found these "transformations" "central to the claims," because "mental steps" of thinking about a dosage adjustment "alone are not patent-eligible."

Pet. App. 19a, 21a. But these changes are not transformative in any meaningful sense, or part of any invention by Prometheus. They are merely the ordinary elements of medical research and treatment. Any physician seeking to improve Prometheus's criteria would inevitably go through the same preliminary steps, so they neither limit the scope of the claims nor prevent them from preempting all uses of the natural correlations.

By once again making these well-known and ubiquitous preparatory steps into the touchstone of patent eligibility, the Federal Circuit ignored the teachings of *Bilski*. This Court held in *Bilski* that while the presence of a "transformation" is a "clue" to patent eligibility, it is not talismanic and does not override the principle that "laws of nature" must be free for all to use. 130 S.Ct. at 3225-3226; see *id.* at 3235 (Stevens, J., concurring), 3258 (Breyer, J., concurring). It stressed too that the antidote to "attempts to call any form of human activity a 'process'" is insistence that claims "mee[t] the requirements of § 101." *Id.* at 3226. And it refused to "endors[e] interpretations of § 101" that the "Federal Circuit has used in the past." *Id.* at 3231. None of those warnings stopped the Federal Circuit from adopting the same analysis as before this Court's GVR, again giving dispositive effect to commonplace transformations and turning a vast swath of ordinary medical practice and research into Prometheus's private fiefdom.

3. The Federal Circuit's decision rests on an indefensible reading of this Court's preemption decisions. It is well established that a patent that preempts all uses of a natural phenomenon does not satisfy Section 101. See *Benson*, 409 U.S. at 71-72 (claim is patent-ineligible when its "practical effect"

is "a patent on the [natural phenomenon] itself"); *Funk Bros.*, 333 U.S. at 130; *Chakrabarty*, 447 U.S. at 309; *LabCorp*, 548 U.S. at 135-136; *Bilski*, 130 S. Ct. at 3230, 3253, 3258. In analogizing Prometheus's claims to *Diehr*, the Federal Circuit made an error that nullifies the distinctions this Court has laid down to guide application of Section 101. Pet. App. 12a. Prometheus merely repeats that error.

The *Diehr* patent recited an algorithm that is a natural phenomenon, but narrowly confined the scope of the patent by reciting a particularized use of the equation to open and close a mold. The patent thus left others completely free to make different uses of the algorithm, with the result that there was no preemption of any natural law. Unlike the patentee in *Diehr*, Prometheus did *not* recite a particular use of the natural correlation. Its patents cover use of that correlation in every manner possible, including by developing criteria that are better than Prometheus's, thinking about why different criteria apply to different diseases, or exploring whether different metabolites can be measured and produce different criteria. They therefore fail the preemption standard set forth in *Benson* and *Flook*, in which claims were invalidated because they covered all uses of the computations.

4. Prometheus incorrectly asserts (at 30-31) that "*LabCorp* presented different issues" from this case. In legally relevant respects, the claims this Court agreed to review in *LabCorp* were identical. And even though Justice Breyer's opinion in *LabCorp* carefully analyzed this Court's relevant precedents and was cited approvingly by five members of the Court in *Bilski* for its substantive discussion of patent law (see Pet. 17-18), the Federal Circuit dismis-

sively "decline[d] to discuss a dissent" or address its analysis of preemption. Pet. App. 16a n.2.

Prometheus argues that the *LabCorp* patent did not involve administering a drug as the initial step of a "process." But the steps in *LabCorp* were testing a patient's body fluid to determine the level of an amino acid, then correlating that level with a deficiency in vitamins "such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at the test result." 548 U.S. at 132. The *LabCorp* claimant argued that, although any test might be used and the correlation was a natural phenomenon, the "process" combining these steps was "an inventive diagnostic test." Oral Arg. Tr., No. 04-607, at 42 (U.S. Mar. 21, 2006). Petitioner there, as here, asked this Court to decide whether patenting this "process" monopolized a basic scientific relationship—a naturally occurring correlation between a substance in the body and patient health.

The initial step Prometheus adds to some claims—a step absent in any event from claim 46—is administration of a drug that Prometheus did not invent. That a synthetic drug is administered and biologically converted does not distinguish this case from *LabCorp*, where tested-for amino acids appeared naturally. Prometheus *concedes* that the difference between synthetic and natural promoters of a biologic change is immaterial. Opp. 30 n.7.

Prometheus has nothing to do with the drug administered, the metabolites into which the body naturally converts the drug, or the blood test used to determine metabolite levels. Those are part of "the storehouse of knowledge." *Funk Bros.*, 333 U.S. at 130. Including these preliminary steps in a "process" is a patent drafter's trick that provides no meaning-

ful distinction between this case and *LabCorp*. See *Diehr*, 450 U.S. at 192 (refusing to "allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection"). As the *LabCorp* dissenters explained, any conduct can be described as a "process" with "a series of steps," but the key legal question is "what those steps embody." 548 U.S. at 137-138. Here, as in *LabCorp*, they embody "a simple natural correlation" and do nothing to reduce the degree to which the claims preempt the use of that correlation. *Id.* at 136-137.

Prometheus also contends (at 30) that the *LabCorp* patent was directed at "observing," while Prometheus's patents are directed at providing "'diagnostic information'" for use in treatment. But the claim in *LabCorp* sought to exert "control over doctors' efforts to use [a natural] correlation to *diagnose* vitamin deficiencies in a patient," and the claimant argued that this was a "useful, concrete, and tangible result." 548 U.S. at 134, 136 (emphasis added). Both here and in *LabCorp*, the controlling legal principle is the same: observing test results to check for natural biologic correlations that inform a physician's diagnosis may not be monopolized by a patent that amounts to "an instruction to read some numbers in light of medical knowledge." *Id.* at 137.

5. Prometheus pretends (at 19-20) that Mayo challenges its patents simply because they include a "mental step." But the mental step in *these* patents broadly precludes thinking about a natural biologic correlation between metabolite levels and patient health. Prometheus's citations are therefore irrelevant. The claim in *Arrhythmia* "d[id] not encompass subject matter transcending what [the claimant] invented." 958 F.2d at 1059. In stark contrast, Prome-

theus admits that its claims foreclose *any* use of the correlation, even when researchers reject Prometheus's numbers (Opp. 27), and even when physicians reject as inappropriate dosage changes suggested by Prometheus's metabolite ranges. Opp. 24. In *Abele*, which upheld a claim that applied an algorithm to CAT scans, the claim did not encompass any mental step, and the court found *un*patentable another claim that preempted all uses of the algorithm. 684 F.2d at 908. And *Griffin* was a patent "interference" dispute over which of two parties invented first, in which Section 101 issues were not asserted or addressed by the court. 285 F.3d 1029.

6. Although this Court granted certiorari to resolve the question six years ago in *LabCorp*—and three Justices urged the importance of deciding the merits "sooner rather than later" (548 U.S. at 134)—Prometheus asserts that resolving it now is "premature." But Prometheus concedes (at 33) that, as the only court with appellate jurisdiction over patent appeals, the Federal Circuit "forge[s] consistent nationwide patent law." See 28 U.S.C. § 1295. The Federal Circuit issued full opinions in this case before and after *Bilski*, reaching the same result and using the same reasoning in each. Its decision is binding on district courts throughout the country, and on the Federal Circuit itself. See *Hometown Fin.*, 409 F.3d at 1365. Because the decision below has immediate nationwide impact—including in cases pending before the Federal Circuit that will now be decided under an incorrect legal standard (see Opp. 32 n.9)—immediate review is warranted. There is nothing to percolate.

Additional considerations make review appropriate now. The issue presented has been fully explored

in the Federal Circuit's opinions, the district court ruling they reversed, the dissenting opinion in *LabCorp*, and numerous amicus briefs on every side of the issue filed in the Federal Circuit and this Court here and in *LabCorp*. The issue is dispositive of this protracted litigation, squarely presented, and free of procedural defects. This case presents the ideal vehicle to decide a question of immense practical importance to healthcare providers, patients, and payors.

7. Nothing in 35 U.S.C. § 287(c)'s narrow exemption from infringement liability for certain "medical or surgical procedures" carried out by a physician addresses the scope of Section 101. Opp. 34; see *Bilski*, 130 S.Ct. at 3228-3229 (statute contemplating "some business method patents" does "not suggest broad patentability" of such methods). And Prometheus never explains how denying a patent for a law of nature that has been dressed up as a "process" by adding a few data gathering steps known to the entire medical profession could interfere with developments in personalized medicine. Opp. 35-36. The AMA warns (at 14) that, to the contrary, such broad patents "would stifle rather than incentivize developments" in this important new field by preempting "scientific observations underlying proper diagnosis and treatment." See Quest Br. 18-20 ("Personalized medicine" uses "genetic markers to predict" disease and "an individual's response to a particular therapy"—just what patents like Prometheus's would foreclose).

Delaying review of the Federal Circuit's faulty approach will adversely affect medical research and patient care, "inhibit[ing]" the exercise of "medical judgment," diverting medical resources to "searching

patent files" to avoid potential treble damages liability, and "rais[ing] the cost of healthcare while inhibiting its effective delivery." *LabCorp*, 548 U.S. at 138. These "special public interest considerations" (*ibid.*) are not theoretical but have immediate practical consequences for the medical profession and the patients it serves, as the AMA and numerous other medical associations attest in their brief urging review (at 9-16). For seven years patients have been denied the benefit of Mayo's test—developed because Mayo believed it more effective than Prometheus's test.

As leading scholars have explained, allowing patents on "abstract ideas," like taking mental note of biologic correlations, leads to claims over ideas "unknown to the inventor" and means "future inventors face *reduced* incentives because they have to obtain a license" to improve upon—or even disprove—the patented correlation. BESSEN & MEURER, PATENT FAILURE, at 199-200. The chilling effect on medical innovation is all the greater because "[t]he notice function" of patents "does not always work" and "[c]learance costs" are high. *Id.* at 8, 10. Indeed, core First Amendment freedoms of physicians and patients are at stake. See Pet. 33-34; ACLU Am. Br. in *Bilski*, No. 2007-1130, at 5-7, 14 (Fed. Cir. Apr. 3, 2008) (a patent like that in *LabCorp* is one "on pure thought or pure speech"). This Court should review the Federal Circuit's erroneous decision to ensure that the Nation's efforts to promote quality healthcare at reasonable cost are not thwarted by sweeping monopolies of basic medicine.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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AMICUS CURIAE BRIEF

No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICI CURIAE* AARP AND PUBLIC PATENT FOUNDATION IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICI CURIAE*[1]

Amici Curiae AARP and the Public Patent Foundation respectfully submit this brief in support of petitioners Mayo Collaborative Services (d/b/a Mayo Medical Laboratories) and Mayo Clinic Rochester (collectively, "Mayo"), encouraging the grant of a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit because that judgment stems from the application of an approach to patentable subject matter that is inconsistent with the Court's precedent and with both health and patent policy. Allowing patents on pure medical correlations (i.e. that an overly high or low level of some chemical in the body correlates to an unhealthy condition) threatens doctors with claims of patent infringement should they discuss mere laws of nature with their patients, burdens the public with excessive health care costs, and dulls incentives for real innovation in medical care.

Amicus AARP is a nonpartisan, nonprofit organization dedicated to addressing the needs and

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[1] In accordance with Supreme Court Rule 37.6, AARP and the Public Patent Foundation state that: (1) no counsel to a party authored this brief, in whole or in part; and (2) no person or entity, other than *amici*, their members and counsel have made a monetary contribution to the preparation or submission of this brief. Counsel of record for all parties received notice at least 10 days prior to the due date of the *amici curiae's* intention to file this brief. The parties have consented to the filing of this brief.

interests of people age 50 or older. AARP has a long history of advocating for access to affordable health care and for controlling costs without compromising quality. Affordable and quality health care is particularly important to the older population because of its higher rates of chronic and serious health conditions. AARP works at the state and national levels for laws and policies that ensure greater freedom and competition in the healthcare marketplace. *See, e.g.*, Stephen Schondelmeyer and Leigh Purvis, *Rx Price Watch Report: Retail Prices for Widely Used Brand Name Drugs Increase Considerably Prior to Generic Competition*, AARP Public Policy Institute, Insight on the Issues 49, March, 2011, *available at* http://assets.aarp.org/rgcenter/ppi/health-care/i49-rx-2011.pdf. AARP supports Petitioners because patents that claim medical correlations prohibit diagnosis and treatment and discourage communication of medical information between a patient and physician.

Amicus Public Patent Foundation ("PUBPAT") at Benjamin N. Cardozo School of Law is a not-for-profit legal services organization that represents the public interest in the patent system, and most particularly the public interest in protecting against the harms caused by undeserved patents and unsound patent policy. PUBPAT provides the general public and specific persons or entities otherwise deprived of access to the patent system with representation, advocacy, and education. PUBPAT has argued for sound patent policy before this Court, the Court of Appeals for the Federal Circuit, various district courts, the United States

House of Representatives, the United States Patent and Trademark Office (USPTO), the United Nations, the European Union Parliament, and other judicial, governmental and political bodies. PUBPAT has also requested that the USPTO reexamine specifically identified undeserved patents causing significant harm to the public. The USPTO has granted each such request. These accomplishments have established PUBPAT as a leading provider of public service patent legal services and one of the loudest voices advocating for comprehensive patent reform.

Amici support this petition for certiorari because of its interest in ensuring that laws of nature are not patented.

REASONS FOR GRANTING THE WRIT

I. This Court Previously Granted Certiorari On The Issue of Whether Medical Correlations Are Patentable, But Did Not Reach It For Procedural Reasons, Making This Case The Proper Vehicle To Address The Issue.

The issue in this case is effectively the same as that previously granted certiorari by this Court in *Lab. Corp. of Am. Holdings v. Metabolite Labs, Inc.*, 546 U.S. 999 (2005) which was:

> Whether a method patent directing a party simply to "correlat[e]" test results can validly claim a monopoly over a basic scientific relationship used in

> medical treatment such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.

This Court ultimately did not reach the issue in *LabCorp*, because the writ of certiorari in that case was dismissed for having been improvidently granted. *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006). In dissenting from the dismissal of certiorari in *LabCorp*, Justices Breyer, Stevens, and Souter noted that, "those who engage in medical research, who practice medicine, and who as patients depend upon proper health care might well benefit from this Court's authoritative answer." The issue of whether medical correlations may be patented is one of supreme importance that merits this Court's attention.

To be sure, the patenting of medical correlations – which are nothing more than expressions of laws of nature – has led to severe restraint on the provision of medical care and a greatly increased cost and reduced availability of vital medical services, damaging the public health of the nation. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 2009 U.S. Dist. LEXIS 101809 (S.D.N.Y. 2009) (owner of patents on medical correlations prevented patients from receiving medical services from physicians).

As just one example, medical correlation patents have been used to prevent patients contemplating surgery to remove their breast and

ovaries from getting independent verification that they have genetic mutations indicating they have an increased predisposition to those diseases. *Id.* at *16-17. Nature created the correlation between genetic mutations and predisposition for disease, not man. Thus, patents on the correlation between certain mutations and an increased risk of breast and ovarian cancer should not be patentable. But such patents are precisely what have been granted. *Id.*

In the years since *LabCorp*, the Federal Circuit has continued to blindly uphold medical correlation patents, without abiding by cases such as *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) where the Court prohibited the patenting of laws of nature. As a result, there are now countless patents on medical correlations, including the patent in this case and patents on correlating genetic mutations with a person's increased risk for a particular disease. *See., e.g., Ass'n for Molecular Pathology*, 2009 U.S. Dist. LEXIS 101809 (involving patents claiming the correlation between mutated BRCA genes and an increased propensity for developing breast cancer). To be sure, under the Federal Circuit's decisions, including this case specifically, one could get a patent on correlating fair skin with an increased risk of sunburn, being a woman with an increased risk of becoming pregnant, and being elderly with an increased risk of suffering from alzheimer's disease.

However, "correlation" patents like these violate the Court's long established precedent that prohibits the patenting of laws of nature.

Chakrabarty, 447 U.S. at 309 (citations omitted). Laws of nature cannot meet the threshold for qualifying as "inventions patentable" under 35 U.S.C. § 101 because "[s]uch discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Id.* (*quoting Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948)). "[T]he reason for the exclusion is that sometimes too much patent protection can impede rather than 'promote the Progress of Science and useful Arts,' the constitutional objective of patent and copyright protection." *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126-27 (2006) (Breyer, J., dissenting).

This Court has repeatedly rejected formulaic rules on issues in patent law, including particularly what constitutes patentable subject matter. *See Bilski v. Kappos*, 130 S. Ct. 3218 (2010) (rejecting the Federal Circuit's "machine or transformation" test for patent eligibility). Despite this, the Federal Circuit below again retreated to implement a formulaic rules-based analysis, finding as patentable subject matter anything that involves a transformation of matter, regardless whether that transformation is central to the patented invention or not. The "administering" step of the claims at issue here is of trivial importance, as there is no requirement that the amount of drug being administered cause any chemical change in the patient to whom the drug is administered. U.S. Patent No. 6,355,623 claim 1 (filed Apr. 8, 1999).

The Federal Circuit latched on to that triviality to uphold the patent as not being a law of nature. This was not a substantive analysis, but rather a formulaic rule that any transformation of matter – no matter how trivial – is sufficient to make a claim patent eligible, regardless of whether the claim still preempts all pragmatic uses of a law of nature. This is wrong public policy and also directly in conflict with the Court's precedent.

Had the Federal Circuit correctly applied the pragmatic preemption analysis, it would unquestionably have found that the claim has the practical effect of preempting all uses of the law of nature that underlies the claim, namely that between the presence of certain metabolite levels and the presence of a drug, and that medical correlation is not an invention of the patentee. It is the result of nature's handiwork and to allow a patent on it, as the Federal Circuit has done, is to allow a patent that denies all use by others of a law of nature until the patent expires.

Now is the time and this is the case to declare that correlations based on laws of nature cannot be patented. The issue has been properly raised and all of the reasons justifying a grant of certiorari in *LabCorp* still exist today. In fact, the issue is perhaps of more importance today than it was several years ago, due to the increased rate at which the Patent Office has granted such patents.

CONCLUSION

For the foregoing reasons, the petition for a writ of certiorari should be granted.

April 20, 2011

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AMICUS CURIAE BRIEF

No. 10-1150

In The Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES)
AND MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Petition For Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF *AMICI CURIAE* THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN MEDICAL ASSOCIATION, THE ASSOCIATION OF PROFESSORS OF HUMAN AND MEDICAL GENETICS, THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, AND THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES IN SUPPORT OF PETITIONERS

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INTEREST OF THE *AMICI CURIAE*

Amici curiae The American College of Medical Genetics, The American Medical Association, The Association of Professors of Human and Medical Genetics, The Association for Molecular Pathology, The College of American Pathologists, and The Association of American Medical Colleges respectfully submit this brief in support of petitioners Mayo Collaborative Services (d/b/a Mayo Medical Laboratories) and Mayo Clinic Rochester (collectively "Mayo") encouraging the grant of a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit, because that judgment stems from an interpretation of patentable subject matter that is inconsistent with this Court's precedent and with public policy regarding both innovation and health care.[1]

Amici are associations of physicians, medical educators, and other providers of healthcare-related services. *Amici* are greatly concerned with the potential impact of the Federal Circuit's decision to allow patenting of claims to natural phenomena such as the

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[1] The parties have consented to the filing of this brief. Counsel of record for all parties received notice at least 10 days prior to the due date of the *amici curiae*'s intention to file this brief. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* and their members or their counsel made a monetary contribution to its preparation or submission.

correlations covered by Prometheus's patents. Such patents have great potential to impede the practice of medicine and raise the costs of medical treatment.

The American College of Medical Genetics (ACMG) is a private, non-profit, voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral level medical geneticists and other physicians involved in the practice of medical genetics. With more than 1,500 members, the ACMG's mission is to improve health through the practice of Medical Genetics. In order to fulfill this mission, the ACMG strives to: 1) define and promote excellence in medical genetics practice and the integration of translational research into practice; 2) promote and provide medical genetics education; 3) increase access to medical genetics services and integrate genetics into patient care; and 4) advocate for and represent providers of medical genetics services and their patients. The position of the ACMG is that observations of naturally occurring correlations should not, in and of themselves, be patentable.

The American Medical Association (AMA) is the largest professional association of physicians, residents and medical students in the United States. Additionally, through state and specialty medical societies and other physician groups seated in the AMA's House of Delegates, substantially all U.S. physicians, residents and medical students are represented in the AMA's policy making process. The objectives of the AMA are to promote the science and art of medicine and the betterment of public health.

The AMA opposes the patenting of medical procedures, as such patents limit the dissemination and utilization of human knowledge.

The Association of Professors of Human and Medical Genetics (APHMG) was incorporated in 1995 as a non-profit organization to promote human and medical genetics educational programs in North American medical and graduate schools. Currently more than 90 medical and graduate schools are members. The APHMG broadly represents the faculty that teach human and medical genetics to virtually all medical students in North America. As educators, they teach medical students to think about, diagnose, and treat genetic diseases. It is the APHMG's position that all physicians must be free to think broadly, creatively, analytically and without fear that they risk infringing a patent merely by *thinking* about the relationship between certain treatments and their potential metabolic and clinical sequelae.

The Association for Molecular Pathology (AMP) is an international medical professional association representing approximately 1,900 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics and genomics. The AMP is dedicated to the development and implementation of molecular diagnostic testing, which includes genetic testing in all of its definitions, in a manner consistent with the highest standards established by the Clinical Laboratory Improvement Amendments, the College of American Pathologists,

the ACMG, and the Food and Drug Administration. AMP members practice their specialty in widely diverse settings, including academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the *in vitro* diagnostic industry, and are involved in every aspect of molecular diagnostic testing. AMP provides national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing.

The College of American Pathologists (CAP) is the world's largest medical society composed exclusively of pathologists, with nearly 18,000 members. Pathologists are physicians who examine tissues, blood, and other body fluids for the purposes of medical diagnosis and patient care. Through its accreditation and proficiency testing programs, the CAP is also a leader in assuring the quality of laboratory testing. More than 7,000 laboratories are accredited by the CAP, and approximately 23,000 laboratories are enrolled in the College's proficiency testing programs.

The Association of American Medical Colleges (AAMC) is a non-profit organization representing all 134 accredited medical schools in the United States, about 400 major teaching hospitals and health systems, and nearly 90 academic and professional societies representing about 125,000 faculty members. AAMC's member institutions are at the forefront of medical education, research and research training, and health care innovation and delivery. AAMC member institutions perform more than half of the extramural research sponsored by the National

Institutes of Health, and they partner with industry in discovering new and better approaches to the diagnosis, treatment, and prevention of human diseases.

SUMMARY OF ARGUMENT

New drugs and new tools for diagnosing illness and monitoring treatment are critical to the advancement of medicine. *Amici* medical associations do not dispute that patents on healthcare-related technologies can enhance the provision of high-quality and cost-effective medical care. The patents at issue in this case, however, do not claim innovative drugs or new diagnostic tools. Instead, these patents grant exclusive rights over the mere recognition that there is a natural statistical correlation between certain metabolite levels in the body, as measured by well-known means, and the potential toxicity and effectiveness of a well-known drug. If these patents remain in force, any physician who measures those metabolite levels, knows of the natural correlation, and thus is "warned" that it might be advisable to adjust the dosage becomes an infringer. This will be the case even if a physician had measured and considered the levels of these metabolites when treating patients prior to the issuance of the patents.

If such claims to exclusive rights over the body's natural responses to illness and medical treatment are permitted to stand, the result will be a vast thicket of exclusive rights in the use of scientific data

that is critical to and must be widely available for providing sound medical care. Conscientious physicians will be unwilling and unable to avoid considering relevant scientific information when reviewing test results. Thus, patent licenses increasingly will be required for physicians to conduct even well-established diagnostic tests. Laboratories will risk indirect infringement merely by educating doctors about the scientific meaning of test results. It is hard to imagine how the clinical diagnostic community will continue to provide quality patient care and how physicians will continue to practice medicine in an ethical and effective manner under such a regime.

Moreover, the claims at issue are not directed to patentable subject matter. These claims run afoul of this Court's longstanding and recently reaffirmed prohibition on the patenting of "laws of nature, physical phenomena, and abstract ideas," under Section 101 of the Patent Act. *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Diamond v. Chakrabarty*, 477 U.S. 303, 309 (1980)). As the district court recognized, the claims at issue here "wholly preempt" the natural relationship between the levels of the metabolites 6-TG and 6-MMP in the human body and the likelihood of therapeutic efficacy and toxicity of thiopurine drugs. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200, 2008 WL 878910 at *10 (S.D. Cal. Mar. 28, 2008) (quoting *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972)).

The Federal Circuit has erred twice in finding that Prometheus's claims encompass patentable subject matter. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 581 F.3d 1336 (Fed. Cir. 2009); *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347 (Fed. Cir. 2010). Even after this Court's remand for reconsideration in light of *Bilski,* the Federal Circuit's analysis was unchanged, continuing to rely heavily on a machine or transformation of matter test. While that test provides a "useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101," *Bilski*, 130 S. Ct. at 3227, it is inapposite to determining whether a patent claim preempts a natural phenomenon or scientific principle. Whether a natural phenomenon involves a "transformation of matter" cannot determine its eligibility for patenting, or virtually every natural phenomenon could be patentable.

The patentability of claims like those at issue here is of great consequence for the future of health care in the United States. The issue was left open by this Court's opinion in *Bilski* and remains unresolved in light of this Court's dismissal of certiorari in *Lab. Corp. of America Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006). The present case provides an appropriate and timely opportunity to resolve this important question.

ARGUMENT

I. Health Care Policy is Best Served by This Court's Well-Established Limits on Patentable Subject Matter, Which Preclude Claims to Observations of Natural Phenomena

The scope of patentable subject matter established by Congress in the Patent Act, 35 U.S.C. § 101, although quite broad, does not extend to scientific facts or observations of natural phenomena. *See Diamond v. Diehr*, 450 U.S. 175, 185 (1981) (citing *Parker v. Flook*, 437 U.S. 584, 593 (1978) and *Benson*, 409 U.S. at 67). The patents at issue here give Prometheus exclusive private ownership not of a new drug, a new diagnostic test, or even a new method of diagnosing a particular disease. Rather, the patents at issue effectively award Prometheus exclusive ownership of a pre-existing diagnostic test based on the mere *observation* of a naturally-occurring phenomenon: the correlation between the levels of certain metabolites produced naturally in the human body in response to administration of certain doses of thiopurine drugs, and the efficacy and toxicity of those drugs.

Amici medical associations recognize that healthcare-related patents can enhance the provision of high-quality and cost-effective medical care. The financial incentive that patents offer supports the expensive and uncertain research required to identify, test, and gain approval for new pharmaceuticals, medical devices, diagnostic testing kits, and other

products. In this respect, the patent system has served patients and the medical profession well.

Patents on scientific observations underlying medical care, however, do not have these salutary effects. Such patents raise ethical concerns for physicians, erode the quality of patient care by limiting use of the very knowledge physicians must rely on to diagnose and treat their patients, and threaten to stifle innovation and raise the costs of medical treatment.

A. Patents on Scientific Observations Raise Ethical Concerns for Physicians

Physicians have longstanding ethical obligations to advance and share useful medical knowledge with patients and other physicians. Principle V of the AMA's Principles of Medical Ethics states, "[a] physician shall continue to study, apply, and advance scientific knowledge," and "make relevant information available to patients, colleagues, and the public. . . ."[2] Opinion 9.08 of the Code of Medical Ethics of the AMA elaborates upon this basic principle:

> Physicians have an obligation to share their knowledge and skills and to report the results of clinical and laboratory research. . . .

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[2] Available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/principles-medical-ethics.shtml (last visited April 13, 2011).

> The intentional withholding of new medical knowledge, skills, and techniques from colleagues for reasons of personal gain is detrimental to the medical profession and to society and is to be condemned.[3]

Basic scientific observations that could be useful to physicians in reaching diagnoses and treating patients or to others in devising medical innovations are quintessential examples of the kind of knowledge that physicians are obliged to share freely. To interpret the patent laws so as to make scientific observations eligible for patent protection threatens to undermine, rather than promote, the ethical practice of medicine.

Physicians also have an ethical obligation to consider the most up-to-date scientific information available when treating their patients. Measurements and observations such as those at issue here are part of the broader clinical evaluation that physicians must undertake when treating patients. It is a routine part of the practice of medicine—indeed, it is essential to meet appropriate medical standards of care—for physicians to monitor metabolite levels and to use those levels along with other laboratory and clinical parameters to guide dosage adjustments, thereby providing necessary and appropriate medical care for their patients.

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[3] Available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion908.shtml (last visited April 13, 2011).

B. Patents on Scientific Observations Erode Physicians' Ability to Provide Quality Patient Care and Burden their Use of Pre-Existing Laboratory Tests

Quality patient care demands that a physician consider test results in light of, among other things, current medical knowledge. Prometheus argued below that a doctor infringes simply by thinking about the correlation between dosage efficacy and toxicity after receiving results of a metabolite test *even if the test was ordered for a reason other than a desire to adjust dosage in light of the limits set out in the patent claims*. Pet. 22. A doctor who had a pre-existing practice of testing levels of the same metabolites would become an infringer if he or she *merely considered what to do about the results in light of relevant scientific information*. There can be no design around a scientific fact. A physician who learns—from the medical literature, colleagues, continuing medical education, or some other source—of the statistical correlation between metabolite levels and drug efficacy and toxicity cannot—and should not—put that knowledge out of mind.

Moreover, if the claims at issue here were properly patentable, a laboratory might induce infringement simply by informing a doctor of the correlation in conjunction with delivery of test results or perhaps even by publishing articles or brochures discussing the correlation. Indeed, confronting very similar facts in *Metabolite Labs., Inc. v. Lab. Corp. of America Holdings*, 370 F.3d 1354 (Fed. Cir. 2004), the Federal

Circuit found that the defendant laboratory had induced infringement through the publication of medical articles.[4] *Id.* at 1365.

The potential ramifications of the Federal Circuit's ruling that such claims are patentable are profound and sobering. By uncovering a correlation between obesity and a particular illness, for example, a researcher could obtain a patent on the process of having a patient step on a scale and then considering that natural correlation in deciding whether to recommend that the patient diet to lose weight. Any entity that made or sold scales and that dared to mention the correlation in a brochure might then be liable for intentionally inducing infringement. An observation that some patients tend to run a particularly high fever if given too much of a particular drug could lead to a patent on taking a patient's temperature and considering whether to raise or lower the dosage with that natural response in mind. Patients, physicians, and thermometer manufacturers might

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[4] This Court is currently considering the state of mind standard for inducement of infringement, *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 458 (2010) (mem.). Though very important in many contexts, the standard is unlikely to be determinative in cases such as this one. Laboratories performing diagnostic tests are highly likely to be aware of broad diagnostic patents, because the patent holders will notify them. Laboratories also generally inform doctors of the scientific significance of test results, and the public health depends on their doing so. Thus, whatever the outcome of *Global-Tech*, diagnostic test laboratories will find it difficult to avoid indirectly infringing the type of claims at issue here.

directly or indirectly infringe because a thermometer reading "warns" that it might be advisable to adjust dosage of the drug.

Such results are unthinkable, yet they are eminently plausible applications of the Federal Circuit's ruling that the claims in this case constitute patentable subject matter. If patent licenses are required for physicians merely to *consider* newly discovered implications of well-established diagnostic tests, and if laboratories become indirect infringers merely by educating doctors about those implications, it is hard to imagine how medical diagnostics will continue to provide quality patient care.

C. Patents on Scientific Observations Threaten to Stifle Innovation, Including the Development of Personalized Medicine

Basic scientific facts are "part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none." *Bilski*, 130 S. Ct. at 3225 (quoting *Funk Bros.*, 333 U.S. at 130). Ensuring wide dissemination of and free access to such facts is essential to scientific progress. Ready access to basic facts, such as a relationship between levels of drug metabolites and the drug's efficacy and toxicity, is essential to medical research. Physicians' understanding of correlations, such as those claimed here, evolves as knowledge of the body's natural responses

to treatment accumulates through medical practice and is shared throughout the medical community.

These patentees are neither the first nor the last to study the implications of these particular metabolite levels for human health. Pet. 5. To improve existing treatment regimens, laboratories such as Mayo continually strive to develop better and less expensive tests of metabolite levels, along with more accurate standards for the clinical interpretation of those levels. Researchers, such as Dr. El-Azhary, seek to study similar correlations so as to understand the body's responses to drugs in different disease contexts and to develop appropriate clinical responses. Pet. 9. Patents such as those at issue here impermissibly burden such medical research, effectively "shut[ting] the door" to scientific progress. *O'Reilly v. Morse*, 56 U.S. 62, 113 (1853).

In addition, patents on scientific observations, such as the statistical correlations involved here, would stifle rather than incentivize developments in medical practice, including the practice of personalized medicine. Such patents, which do not cover inventive diagnostic tests but instead seek to preempt the scientific observations underlying proper diagnosis and treatment, threaten to slow the development of diagnostic testing and undermine competition to provide inexpensive and high quality testing, leading inevitably to higher-priced medical treatment.

Moreover, patents are not needed to incentivize physicians and researchers to study the kinds of

clinical correlations at issue in this case. For example, the Secretary's Advisory Committee on Genetics, Health, and Society conducted an extensive investigation into the need for patents in the context of genetic diagnostic testing and found:

> [P]atents do not appear to be necessary to stimulate research and genetic test development. . . . [S]cientists are principally motivated to conduct research by their curiosity, career ambitions, and desire to advance understanding of health and disease. . . . Similarly, laboratories have sufficient non-patent incentives to develop genetic tests: clinical need and demand drive development, and development costs are minimal.[5]

Patents are equally unnecessary to stimulate research and development of the diagnostic methods claimed here. Academic researchers and clinicians do not need patents to motivate them to study the scientific correlations between metabolite levels and the body's responses to treatment. Development costs for these diagnostic tests are also low, in part because approval of such tests does not involve the high regulatory costs involved in the development of pharmaceuticals and medical devices. Exclusive

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[5] Secretary's Advisory Committee on Genetics, Health, and Society, *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* (April 2010) at 90, *available at* http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf (last visited April 13, 2011).

rights do not promote innovation in this context. On the contrary, when scientific knowledge of the medical implications of clinical tests is freely available there is enormous incentive for physicians to *make use of that knowledge* to provide necessary and appropriate care for their patients.

II. Because the Claims Asserted in this Case Impermissibly Preempt Natural Phenomena, the Ruling Below is Inconsistent with This Court's Precedents

A. The Asserted Claims Are Directed to Natural Phenomena

The claims at issue here seek to patent the statistical observation that some doses of thiopurine drugs tend to be too high for some patients and some tend to be too low. These claims run afoul of time-honored prohibitions on patenting "laws of nature, physical phenomena, and abstract ideas," *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 477 U.S. at 309), because they "wholly preempt" the natural relationship between the levels of the metabolites 6-TG and 6-MMP in the human body and the likelihood of therapeutic efficacy and toxicity of thiopurine drugs. *Prometheus*, 2008 WL 878910 at *10 (quoting *Benson*, 409 U.S. at 71-72).

Any argument that the observed correlations between metabolite levels and drug toxicity are patentable because the metabolites are by-products of a synthetic drug is inconsistent with precedent and

would lead to absurd results. In patent law, "natural" means "nature's handiwork" as generally juxtaposed with the products of human agency and ingenuity. *See Chakrabarty*, 447 U.S. at 310; *Flook*, 437 U.S. at 591-94. Thiopurine drugs are man-made compositions of matter, undeniably patentable under 35 U.S.C. § 101. A natural response to a man-made invention, however, has never been patentable. In *Funk Brothers*, for example, the patentee combined laboratory cultures of selected bacteria to form an "inoculant" that assisted nitrogen fixation in plants. *Funk Bros.*, 333 U.S. at 129. Despite the human effort required to select, culture, and combine the bacteria, this Court found the mixture unpatentable because the mutual non-inhibition of nitrogen fixing properties was a natural response to being combined. Though the combination was artificial, the bacteria "serve[d] the ends nature originally provided and act[ed] quite independently of any effort of the patentee." *Id.* at 131.

This distinction between a man-made product and its natural behavior has long been recognized. In *O'Reilly v. Morse*, for example, this Court discussed the English case, *Neilson v. Harford*, 151 E.R. 1266 (1841), and distinguished between the unpatentable "principle that hot air will promote the ignition of fuel better than cold" and the patentable invention of a mechanical apparatus for supplying hot air. *O'Reilly*, 56 U.S. at 114-16. Any invention involving igniting fuel in a furnace is in some sense synthetic, yet that fact would not have rendered patentable a claim to

the principle of using hot air to aid ignition. Nor did the fact that printing characters at a distance is a human endeavor save a claim to the basic scientific concept of using "the motive power of the electric or galvanic current" to make such characters. *Id.* at 119.

The district court in this case correctly concluded that "the relevant inquiry is whether the correlations are 'man-made,' not whether a man-made drug was used to produce the correlation." *Prometheus*, 2008 WL 878910 at *9. Here, the claimed correlations between drug metabolite levels and drug toxicity and efficacy are natural phenomena. Nothing in the claims purports to affect the way in which a patient's body responds to the administration of the medications: the phenomena are merely observed.

Because the claimed statistical correlations are natural phenomena, the claims are unpatentable, since they wholly preempt every substantial use of those correlations. The claims cover every instance in which any physician considers whether to adjust thiopurine drug dosage in light of metabolite level measurements. *Id.* at *10. These claims are unlike those in *Diehr*, 450 U.S. at 180, n.5, to which the Federal Circuit analogizes them. *Prometheus Labs.*, 628 F.3d at 1355. The claims in *Diehr* were directed to "a physical and chemical process for molding precision synthetic rubber products . . . beginning with the loading of a mold with raw, uncured rubber and ending with the eventual opening of the press at the conclusion of the cure," *Diehr*, 450 U.S. at 184, which employed a mathematical formula to

determine when to open the press. The claims in this case are different. They do not *apply* a natural phenomenon as part of a patentable process. Rather, they merely instruct one to measure a natural phenomenon and then consider its implications.

B. The "Transformation of Matter" Inquiry is Unhelpful in Determining Whether a Claim is Directed to Unpatentable Natural Phenomena

Both before and after the remand for reconsideration in light of this Court's opinion in *Bilski*, the Federal Circuit focused the bulk of its attention on applying the machine or transformation of matter test. *Prometheus Labs.*, 628 F.3d at 1355-56; *Prometheus Labs.*, 581 F.3d at 1345-46. As this Court held in *Bilski*, that test is "a useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101." *Bilski*, 130 S. Ct. at 3227. It is inapposite, however, to determining whether a claim preempts a natural phenomenon. Photosynthesis, the freezing of water into ice and its evaporation into steam, and the rusting of iron—all involve transformations of matter, but are unpatentable unless they are part of an invention that does not preempt the phenomenon. Moreover, virtually any measurement of a natural phenomenon involves some material transformation. Nonetheless, measuring a natural phenomenon and

then considering its scientific or medical significance does not turn it into patentable subject matter.

This Court should clarify that, whatever the usefulness of the machine or transformation of matter test in determining the patentability of some kinds of processes, such as the abstract hedging methods in *Bilski*, 130 S. Ct. at 3229, the fact that a natural phenomenon involves a material transformation does not render it patentable.

III. The Issue Raised in this Case is of Great Importance and is Left Open After This Court's Ruling in *Bilski*

As argued throughout this brief, the potential for patents that preempt natural phenomena to interfere with the ethical and effective practice of medicine and with the improvement of health care through advances in diagnostic testing is a very serious matter. Exclusive rights to fundamental information about scientific correlations are liable to raise the cost of medical care prohibitively without compensating benefits to medical research. As health care professionals, we believe that patients are served best by the free and broad dissemination of scientific information that is relevant to providing better and more personalized health care treatments. If this Court lets the Federal Circuit's ruling stand, patients, physicians, and laboratory service providers will become entangled in a growing thicket of patents on basic

diagnostic information to the detriment of the nation's health.

This Court granted certiorari to address this issue in *Lab. Corp. v. Metabolite*, though certiorari was later dismissed as improvidently granted because the patentable subject matter issue was not properly considered by the lower courts. *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 132-33 (2006) (Breyer, J., dissenting). Here this Court has the benefit of full exploration of the issue in a considered district court opinion and two Federal Circuit opinions which were informed by extensive briefing by both parties and numerous *amici*.

In *Bilski*, this Court reaffirmed the time-honored patentable subject matter exceptions for "laws of nature, physical phenomena, and abstract ideas," noting that these subject matters are "free to all men and reserved exclusively to none." *Bilski*, 130 S. Ct. at 3225 (quoting *Funk Bros.*, 333 U.S. at 130). The patent claims at issue in this case raise important questions concerning the patentability of natural phenomena and scientific correlations that were not aired in *Bilski* because of its focus on the appropriate standard of patentability for business methods and similar processes. We thus contend that this case warrants the attention of this Court.

CONCLUSION

For the foregoing reasons, the petition for writ of certiorari should be granted.

Respectfully submitted,

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JOINT APPENDIX

RECORD
AND
BRIEFS

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No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

JOINT APPENDIX – VOLUME 1

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PETITION FOR CERTIORARI FILED MARCH 17, 2011
CERTIORARI GRANTED JUNE 20, 2011

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IN THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF CALIFORNIA

No. 04-CV-1200

Prometheus Laboratories, Inc., Plaintiff,

v.

Mayo Collaborative Services (d/b/a Mayo Medical Laboratories) and Mayo Clinic Rochester, Defendants.

RELEVANT DOCKET ENTRIES

NO.	DATE	DESCRIPTION
1	06/15/04	Complaint for Patent Infringement filed by Plaintiff
139	08/09/05	Memorandum in Support of Motion for Summary Judgment of Infringement filed by Plaintiff
166	08/19/05	Memorandum in Opposition to Plaintiff's Motion for Summary Judgment filed by Defendants
227	11/22/05	Order Denying Defendants' Motion for Summary Judgment of Non-Infringement and Granting Plaintiff's Cross-Motion for Summary Judgment of Infringement

NO.	DATE	DESCRIPTION
267	04/14/06	Second Amended Complaint for Patent Infringement filed by Plaintiff
277	04/18/06	Answer and Counterclaims to Second Amended Complaint filed by Defendants
502	01/29/07	Memorandum in Support of Motion for Summary Judgment of Patent Invalidity under 35 U.S.C. § 101 (and Supporting Declarations) filed by Defendants
528	02/28/07	Memorandum in Opposition to Defendants' Motion for Summary Judgment of Patent Invalidity under 35 U.S.C. § 101 (and Supporting Declarations) filed by Plaintiff
539	03/08/07	Memorandum in Support of Motion for Summary Judgment of Infringement filed by Plaintiff
542	03/09/07	Reply Memorandum in Support of Motion for Summary Judgment of Patent Invalidity under 35 U.S.C. § 101 (and Supporting Declarations) filed by Defendants

NO.	DATE	DESCRIPTION
561	04/12/07	Memorandum in Opposition to Plaintiff's Motion for Summary Judgment of Infringement filed by Defendants
598	03/28/08	Order Granting Defendants' Motion for Summary Judgment of Patent Invalidity under 35 U.S.C. § 101
600	05/16/08	Final Judgment
601	05/30/08	Notice of Appeal filed by Plaintiff

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

No. 2008-1403

Prometheus Laboratories, Inc., Plaintiff-Appellant,

v.

Mayo Collaborative Services (d/b/a Mayo Medical Laboratories) and Mayo Clinic Rochester, Defendants-Appellees

RELEVANT DOCKET ENTRIES

NO.	DATE	DESCRIPTION
96	08/05/09	Argued and Submitted
	09/16/09	Opinion Reversing Judgment Below. Judgment entered.
109	06/29/10	Order of the Supreme Court granting certiorari, vacating the judgment, and remanding to the court of appeals
119	09/01/10	Order Denying Petition by Defendants-Appellants for Hearing En Banc on Remand from the Supreme Court
	12/17/10	Order Reversing Judgment Below. Judgment Entered.
133	06/20/11	Order of the Supreme Court granting certiorari

[Deposition of Chuck Kroll, filed August 9, 2005]

[Caption omitted in printing]

* * *

[Tr. 148] Q. Do you see on Mayo 2344 where it says therapeutic range 6-TGN 235 to 400?

A. Yes.

Q. Where did that come from, sir? * * *

A. I don't recall. * * *

Q. Sir, according to this document it appears that Mayo uses a therapeutic range of 235 to 400 picomoles times per 8x10 to the eighth cells for 6-Thioguanine; isn't that correct, sir? * * *

[Tr. 151] A. This document appears to be information that was sent to Dr. El-Azhary in regard to this set of patient samples alerting her to the possibility that some of these patients might require a look—looking at the dates on these samples. These were samples that were collected over three to four months, and in the patient's interest, she was alerted or this was an attempt to alert her that those values seemed abnormal according to literature values.

Q. What literature values are you referring to, sir?

A. The ranges that are the therapeutic ranges that are stated here.

Q. And what literature are you referring to, sir?

A. The literature that we would have done through the literature searches. According—looking

at the dates on these samples, this form was probably prepared mid-February, before any decision had been made on therapeutic ranges for the Mayo test. And exactly where those ranges came from, I cannot exactly say. It is not referenced here where they came from. And in no sense [Tr. 152] was this form meant to be that inclusive at that time.

Q. So for these dermatological patients Mayo Clinic received a blood sample, determined the level of 6-Thioguanine in the blood sample of that patient, and then provided that information to Dr. El-Azhary with a therapeutic range for 6-Thioguanine between 235 and 400 picomoles per 8x10 to the eighth cells; is that correct? * * *

A. This is a form that I created. Therapeutic range is from literature. Knowing that she was doing a dermatological study, not an irritable bowel study, not a Crohn's disease study. Basically it was the best information we had at the time.

[Deposition of Dietrich Matern, M.D., filed August 9, 2005]

[Caption omitted in printing]

* * *

[Tr. 15] Q. What is the purpose of the implementation notice, which is the first page of Plaintiff's Exhibit 29?

A. The purpose of an implementation notice that announces a new test is basically to make clients of Mayo [Tr. 16] Medical Laboratories aware of the new test that is going to be implemented.

Q. And when you refer to "clients," what are you referring to, sir?

A. I am sure you can ask Mayo Medical Laboratories who their clients are, but they are typically hospitals and other laboratories in the country, in the world who may require testing through Mayo Medical Laboratories.

Q. So clients are not limited to just Mayo physicians; is that correct?

A. No.

Q. Who were the intended clients for the Azathioprine metabolites profile as of the date of the implementation notice, sir?

A. Physicians who are treating patients with Azathioprine and are interested to know what the metabolite levels are in their patients' blood cells.

Q. So the purpose of the implementation notice, Plaintiff's Exhibit—the first page of Plaintiff's Exhibit 29, is to notify the public of the availability of a new test?

A. I—I wouldn't say it is the public, but I mean it goes to the clients of Mayo Med Labs, and I don't know what the clients told you with those implementation notices, but as far as I know, this is not posted in an [Tr. 17] ad in Newsweek.

Q. So the purpose of the implementation notice then, Plaintiff's Exhibit 29, the first page of Plaintiff's Exhibit 29, is to notify Mayo clients of the availability of a new test; is that correct?

A. Yes.

* * *

[Tr. 170] Q. What were the factors that motivated Mayo Clinic to develop an in-house test for Azathioprine metabolites? * * *

[Tr. 171] A. Again, as I said earlier, we are always trying to improve on patient care, and because it was felt that there was room for improvement with regard to at least the turnaround time to doing the test in-house as opposed to sending it around in the country, that is certainly a major reason to – to develop testing here or modify the testing already to do.

Q. Are there any other reasons why Mayo wanted to develop an in-house version of the Azathioprine metabolites profile?

MS. BUSH: Same objections.

A. As I mentioned earlier that obviously Mayo Medical Laboratories preferred us to have the test here for their reasons, but again, we are not letting us be pushed by Mayo Medical Laboratories unless we really see a reason for patient care to do it in-house.

Q. And what were the reasons for the Mayo Medical Lab?

MS. BUSH: Same objections.

A. I mentioned earlier that they are sometimes concerned about a high volume of testing going through their lab or through the—through the lab, and not staying at Mayo, as opposed to having the test done here.

Q. Why would Mayo Medical Labs be concerned about [Tr. 172] high volume of testing going through their lab and out to outside reference labs instead of staying at Mayo?

MS. BUSH: Lacks foundation, calls for speculation, not relevant to infringement or claim construction.

A. I think Mayo Medical Laboratories as a for profit would be interested to rather get the reimbursement to stay with Mayo Medical Laboratories as opposed to having to pay somebody else to do the test.

* * *

[Deposition of Dr. John F. O'Brien, filed August 9, 2005]

[Caption omitted in printing]

* * *

[Tr. 18] Q. Do you know a Dr. Curtis Hanson?

A. I do, yeah.

Q. And did Dr. Curtis Hanson play any role whatsoever in the TGN procedure?

MS. BUSH: Object to the form.

A. He's aware of its development and thought it would be a useful tool.

Q. (By Mr. Hostetler) And how do you know he was aware of the TGN procedure?

A. During its development early he had a meeting with me and suggested it was a good project.

Q. And who is Dr. Curtis Hanson?

A. He is the head of the department of laboratory medicine.

* * *

[Tr. 20] Q. And what do you recall about what Dr. Curtis Hanson said at this meeting on the TGN procedure?

A. He said that it was relatively high priority for development.

Q. Did he provide a basis for why he thought it should be relatively high priority?

A. Only a business basis.

Q. And what is that business basis?

A. There were recordable numbers of samples being sent out and so we usually respond. That's a typical measure of—a business measure for development. That is not always the only measure of our developmental effort. The clinical importance in my mind is more important.

Q. But you recall Dr. Curtis Hanson providing a business basis as his reason for why the TGN procedure was of relatively high priority; is that correct?

A. That's true.

Q. And you said that your call—the business basis being that there were a reportable number of samples being sent out of Mayo. What did you mean by that?

[Tr. 21] A. Well, all samples passed on are enumerated without regard to the test. And this one it was suggested there was a reasonable number.

Q. Do you recall the number?

A. No.

Q. Approximately?

A. No.

Q. And when you say the samples were being sent out of Mayo, what do you mean by that?

MS. BUSH: Objection, foundation.

A. Not out of Mayo. Out of Mayo Medical Laboratories. This is an accounting procedure of Mayo Medical Laboratories, not Mayo.

Okay, after clarifying that I've forgotten the question.

Q. (By Mr. Hostetler) Sure, no problem. You had indicated that the basis for Dr. Curtis Hanson's business reason for providing a high priority to the TGN procedure was that a reportable number of samples were being sent out of MML and I was wondering what you meant by being sent out of MML.

MS. BUSH: Objection, foundation.

A. Oh. They were being referred to another laboratory.

* * *

[Tr. 56] Q. If you could look at Plaintiff's Exhibit 29 which is [Tr. 57] in front of you, sir. Were you aware that MML had a desire to offer an azathioprine metabolites profile?

MS. BUSH: Object to the form.

A. Definition of the test is probably in order. I knew that they were interested in offering a test that would define TGN numbers.

Q. (By Mr. Hostetler) Okay. And why were they interested in offering such a test?

MS. BUSH: Objection, foundation.

A. Why was who?

Q. (By Mr. Hostetler) Do you know why—. You said you knew that MML was interested in offering a test for measuring TGN levels and I'm asking: Do you know why they were interested?

MS. BUSH: Objection, foundation.

A. I think we stated that earlier.

Q. (By Mr. Hostetler) I don't recall asking—. Was the reason offered by Dr. Curtis Hanson? Is that the reason?

MS. BUSH: Object to the form.

Q. (By Mr. Hostetler) What was the reason, sir?

A. The reason—

MS. BUSH: Objection, foundation.

A. The reason was a business consideration by Mayo Medical Laboratories.

[Tr. 58] Q. (By Mr. Hostetler) Okay.

A. I think—is that what you understood from our previous discussion?

Q. I knew that that's what Dr. Curtis Hanson's opinion was and I didn't realize that that was your understanding of why MML itself wanted to also offer the test for measuring TGN levels.

MS. BUSH: Object to the form.

Q. (By Mr. Hostetler) So that's why I was asking it, sir. Why was the department of laboratory medicine and pathology interested in offering a test for measuring TGN levels in patient samples?

MS. BUSH: Objection, foundation.

A. We're the technical wing of Mayo Med Labs.

Q. (By Mr. Hostetler) And any other reason?

MS. BUSH: Same objection.

A. Not that I know of.

* * *

[Reporter's Transcript of Summary Judgment Motion Hearing on Infringement, September 29, 2005]

[Caption omitted in printing]

For Plaintiff: Wilson Sonsini Goodrich, et al. Alexandra Mahaney, Esq.

* * *

[Tr. 4] The Court: * * * We're here today on cross-motions. First, we have defendant's motion for non-infringement, and then the plaintiff's motion for infringement.

* * *

[Tr. 41] [Ms. Mahaney:] And the last one, the level indicates a need to decrease subsequent doses, the level is a sign, an indication that the subsequent doses should be decreased or even maybe need to be decreased. It doesn't require an actual decrease, and it doesn't require an instruction to the doctor to decrease. All that's required is that the level is an indication or a sign that the dose needs to be decreased.

* * *

[Second Amended Complaint for Patent Infringement, filed Apr. 14, 2006]

[Caption omitted in printing]

* * *

6. PROMETHEUS alleges that MML and MAYO CLINIC have infringed and continue to infringe the '623 Patent directly, contributorily, and by inducement of others, by making, using, selling, importing and/or offering for sale methods covered by the '623 Patent. MML and MAYO CLINIC are liable for patent infringement pursuant to 35 U.S.C. § 271.

* * *

11. PROMETHEUS alleges that MML and MAYO CLINIC have infringed and continue to infringe the '302 Patent directly, contributorily, and by inducement of others, by making, using, selling, importing and/or offering for sale methods covered by the '302 Patent. MML and MAYO CLINIC are liable for patent infringement pursuant to 35 U.S.C. § 271.

[Deposition of Dr. Yves Théorêt, filed Jan. 29, 2007]

[Caption omitted in printing]

* * *

[Tr. 21] Q. Isn't it true that thiopurine metabolites in red blood cells have been tested for many, many years prior to the patents-in-suit?

* * *

A. So, I answer?

Q. You may answer, yes.

A. It has been done in other places, yes.

* * *

[Deposition of Ernest Seidman, filed Jan. 29, 2007]

[Caption omitted in printing]

* * *

[Tr. 103] Q. What do you mean by you discovered that therapeutic efficacy was generally associated with 6-TGN metabolites concentrations greater than about 400?

A. As I mentioned to you, in a database of patient's information which included complications of thiopurine drug therapy, amongst which the most important is myelo-toxicity and going through the patient outcomes and our data, we felt that the risk of myelo-toxicity was associated with 6-TGN metabolite concentrations about four hundred (400).

Q. You felt that or you discovered that toxicity was generally associated?

A. We discovered that from our data centre.

* * *

[Tr. 104] Q. Okay. And that general association was something you found in the patient population that you studied?

A. Correct.

[Tr. 105] Q. And you believe that association exists in a patient population today?

A. I do.

Q. And you believe that you and Dr. Théorêt discovered that correlation, excuse me, that association?

A. Yes, in inflammatory bowel disease.

Q. And others had failed to recognize that association before you and Dr. Théorêt, is that true?

Mr. MICHAEL J. HOSTETLER:

Objection of form, vague. Okay.

A. I'd have to go back to the literature at the time. I believe that the studies that had done. . . had been done previously were in children with leukemia.

And the toxicity in leukemia is really very distinctive from patients with. . . disease.

* * *

[CR20 Submission Template, filed Jan. 29, 2007]

Title of the study:	**Development of biochemical and drug monitoring parameters for use in dermatological patients treated with azathioprine: expanding the thiopurine methyltransferase paradigm.**
Principal investigator:	**Rokea A. el-Azhary, M.D., Ph.D.**
Co-investigator(s):	**O'Brien, John Ph.D., Sandborn W. M.D.**
Statistician:	**Weaver, A. M.S., Bergstahl E. M.S.**

Abstract

Management of dermatological patients treated with azathioprine (AZA) in Dermatology has been dependent on measuring the activity of the enzyme thiopurine methyltransferase (TPMT) prior to treatment to determine the initial dose (1,2). It is well established that TPMT is an enzyme that exhibits genetic polymorphism and is the enzyme most responsible for determining the azathioprine induced "idiosyncratic" and potentially fatal hematopoietic toxicity (3,4,5). The wild type enzyme is present in 90% of the population who can therefore tolerate standard doses of AZA. About 10-11% of the population is heterozygous and significant dose reductions are necessary. Another 0.3% are homozygous mutants and may not tolerate any dose of AZA (6,7).

Over the past 30 years dermatologists have been using azathioprine as a first line steroid sparing

agent to treat several dermatological disorders including immunobullous diseases, pyoderma gangrenosum, atopic dermatitis and others (8-17).

Initial dosage of AZA has been established in 1995 by Snow and Gibson (1,2) via a retrospective study of 28 patients treated with AZA. Since then there have been no other studies to determine monitoring guidelines. Recent literature has shown that monitoring the level of the 6-thioguanine nucleotides (6-TGN), the active metabolites of AZA may be a better prognosticator of therapy and toxicity (18-21). In addition, some studies (but not all) have reported that TPMT is an inducible enzyme (22,23), thus reliance on a one-time measurement of the enzyme activity (phenotype) for establishing the dose may not be sufficient.

We propose a prospective clinical trial to establish a therapeutic "drug level" for AZA based on monitoring the level of its active metabolites 6-TGN and the inactive metabolite 6-methylmercaptopurine (6-MMP) in RBC and correlating those levels with clinical response and side effects.

Research Plan

I. Specific Aims

The primary aim is to establish a therapeutic range for the active metabolites 6-TGN below which there may be therapeutic failure and above which hematological toxicity may occur in patients with dermatological diseases.

* * *

[Deposition of Rokea el-Azhary, M.D., filed Jan. 29, 2007]

[Caption omitted in printing]

* * *

[Tr. 110] Q. When you—strike that. I will start over again.

During the time that you conducted your derm study, were you aware that other investigators had determined that the therapeutic range for 6-TGN levels in patients who were receiving azathioprine and were IBD patients was between about 230 and 400—

* * *

Q. —picamoles per eight times ten to the eighth RBCs?

* * *

THE WITNESS: If you look at my protocol here in my paper that I wrote in 2002, you will see that I [Tr. 111] have quoted what was out in the literature, which was in transplant patients being about 100, and the level in IBD patients was about 200 and something.

That was the level that I was aware of. And that is the whole premise of my protocol is that that does not necessarily apply to dermatologic diseases. If you can see a difference in transplant individuals and a difference in IBD, which are really essentially the same thing, there is no reason to extrapolate, there is no reason to extrapolate to dermatology. That is the whole premise of this study. Is that even if I knew of any of those doses around there, they were irrelevant to my study.

[Expert Report of Dr. Richard Bloomfeld, excerpts filed Jan. 29, Mar. 8, Mar. 9, 2007]

[Caption omitted in printing]

* * *

15. The '623 and '302 Patents describe methods for optimizing the response or reducing the toxicity of patients who are being treated with thiopurine drugs, such as azathioprine and 6-mercaptopurine. The key therapeutic aspect of such thiopurine drugs is that they are converted naturally by enzymes within a patient's body to form an agent that is therapeutically active; in other words, thiopurine drugs are metabolized to form an "active metabolite" that then treats the patient's disease.

* * *

A. The Derm Study

54. In April 2002, three of Mayo's scientists—Drs. el-Azhary, O'Brien and Sandborn—submitted a grant proposal and protocol to Mayo for approval and funding. [Exh. 347] This proposal was rejected, but a second grant proposal filed in August 2002 was approved for funding by Mayo.[16] [Exh. 346] In this Derm Study, the study subjects were patients with a non-IBD autoimmune disease (specifically, "an autoimmune immunobullous disease including bullous pemphigoid and pemphigus vulgaris" [Id. at MCR003195]) who will "be treated with azathioprine by their physicians." [Id.]

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[16] In this second grant proposal, the three original Mayo scientists were joined by a fourth Mayo scientist, Dr. O'Kane.

55. Further, according to this approved Derm Study, a sample of whole blood was to be drawn at least 9 times from each patient for testing metabolite and TPMT levels: a first "baseline" sample, and then 8 further samples over the next year as the patient returned to Mayo for disease evaluation and (if appropriate) dose adjustment of azathioprine. [Id. at MCR003196] Dr. O'Brien's lab (which is the same lab that developed Mayo's test) was tasked with measuring the 6-TG and 6-MMP levels in each sample of blood obtained from a patient enrolled in the Derm Study. [Id.]

56. Between March 2004 and June 2006, the Derm Study samples were analyzed by Charles Kroll, the technologist at MCR who also developed Mayo's test. He then sent the results to the Derm Study investigators, Dr. O'Brien [Exh. 200] and Dr. el-Azhary [Exh. 21] With his first data set, sent in March 2004, Mr. Kroll added the note that the "Therapeutic Range" for 6-TG was "235-400." [Exhs. 21 & 200]

57. After providing his warning with the first set of Derm Study patient data, Mr. Kroll subsequently sent Dr. O'Brien and Dr. el-Azhary, on a periodic basis, further sets of 6-TG and 6-MMP levels for the Derm Study patients. [Exhs. 62, 77-88] Although these subsequent sets of results did not expressly repeat his warning regarding that the "Therapeutic Range" for 6-TG was "235-400," he provided no information that altered or contradicted this warning. Therefore, in my opinion, the warning applied and stayed the same for all patient results provided by Mr. Kroll.

58. The 6-TG and 6-MMP levels for the Derm Study samples were measured in red blood cells us-

ing high-performance liquid chromatography by the same methods that Mayo planned to use with its own commercial test (i.e., Mayo's test). [Exh. 16]

B. The Derm Study Meets Each and Every Limitation of Claim Set 2[17]

* * *

60. A "subject having said non-IBD autoimmune disease": Claims 22, 24 and 35 of the '302 Patent in Asserted Claim Set 2 all require that the subject in the method have a "a non-IBD autoimmune disease." In my opinion, this element is literally found in the Derm Study because the protocol for the Derm Study requires all subjects to have an autoimmune immunobullous disease including bullous pemphigoid and pemphigus vulgaris." [Exh. 346 at MCR003196] Such autoimmune diseases fall within the definition of non-IBD autoimmune diseases provided in the Patents. [Exh. 13 at 14:58-15:54] Thus all subjects in the Derm Study had a non-IBD autoimmune disease.

* * *

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[17] Although not necessary for my analysis, I want to emphasize that over 400 samples were tested by MCR during the Derm Study and that the results of the Derm Study were used to validate and train technologists on how to perform Mayo's test, i.e., the commercial test that Mayo intended to replace Prometheus' Test. [See, e.g., MML 30(b)(6) (5/25/2005) Dep. Tr. at 157:9-158:22]

[Appendix B to Bloomfeld Report]

INTERPRETATION OF ASSERTED CLAIM SETS 1 AND 2

U.S. Patent No. 6,355,623	
1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder comprising (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and	1. A method comprising: (a) administering to a subject a drug that is metabolized to 6-TG wherein the subject has an immune-mediated gastrointestinal disorder;
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,	(b) determining the level of 6-TG in the subject;
wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and	wherein any level of 6-TG below 230 (+/- 15%) pmol per 8 x 10^8 red blood cells is a warning that increases in future doses of drug may be required, and

wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	wherein any level of 6-TG above 400 (+/-15%) pmol per 8 x 10^8 red blood cells is a warning that decreases in future doses of drug may be required.

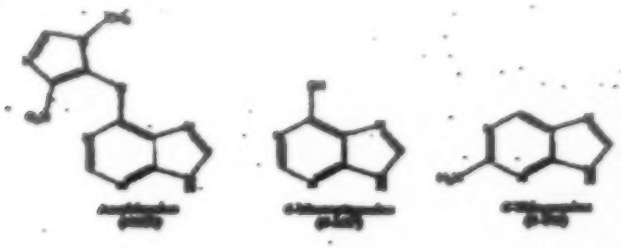
[Rebuttal Expert Report of Dr. Stephen B. Hanauer, filed Feb. 28, 2007]

[Caption omitted in printing]

* * *

A. Overview of Drugs That Deliver 6-Thioguanine

32. Drugs that deliver 6-thioguanine nucleotide (thiopurine drugs) are widely used for their cytotoxic and immunosuppressive properties. These drugs include 6-mercaptopurine (6-MP), azathioprine (AZA), 6-methylmercaptopurine (6-MMP) and 6-thioguanine (6-TG).



33. Drugs that deliver 6-thioguanine nucleotides are synthetic drugs, *i.e.* are man-made drugs that do not occur naturally. Azathioprine is a prodrug of 6-MP, which means that upon administration to a patient azathioprine is converted to 6-MP by splitting off its imidazole group. 6-MP is metabolized to the pharmacologically active 6-thioguaninenucleotides (6-TGN) and 6-methylmercaptopurine ribonucleotides (6-MMP). The 6-TGNs are purine necleotides, which are incorporated into the DNA of leucocytes, inducing immunosuppression. Drugs that deliver 6-thioguanine work over time, and in the setting of inflammatory bowel disease, it generally takes 3-6

months for the drug to demonstrate clinical benefits when administered orally. But for the administration of man-made thiopurine drugs, the thiopurine metabolite (6-TGN and 6-MMP) would not exist in the body.

34. Although the immunosuppressive properties of drugs that deliver 6-thioguanine are still incompletely understood, there are several potential mechanisms of action. Toxicity due to metabolites of drugs that deliver 6-thioguanine may be explained by polymorphisms of the gene encoding thiopurine *S*-methyltransferase (TPMT), the enzyme that methylates 6-MP to 6-MMP. In the case of reduced enzyme activity, toxic 6-TG levels may occur with minimal doses of azathioprine or 6-MP. In some patients with normal or high production of TPMT, 6-MP is largely transformed into 6-MMP while 6-TG levels remain subtherapeutic. Elevated levels of 6-MMP may increase the risk of toxic side effects such as hepatitis.[10]

35. The active metabolites of the thiopurine drugs, 6-TGN and 6-MMP, can be quantified in the human red blood cells by a technique called reversed-phase high-performance liquid chromatography (HPLC). Red blood cells are used because they can be easily obtained in large quantities from whole blood and reflect 6-TGN concentrations that mimic the 6-TGN concentrations in the target cells of the thiopurine drug, *i.e.*, leucocytes.

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[10] *See, e.g.*, Exh. 308.

B. Drugs That Deliver 6-Thioguanine Are Used To Treat A Variety Of Different Diseases

36. Although the Federal Food and Drug Administration (FDA) has not approved marketing azathioprine or 6-MP for use in any disease other than leukemia, drugs that deliver 6-thioguanine are used to treat a variety of different diseases with significantly different clinical endpoints. This is because azathioprine/6-MP are non-specific immunosuppressants whose primary targets are leucocytes. As immunosuppressants, thiopurine drugs are used in the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, and other inflammatory autoimmune diseases.

37. Although I will discuss a number of different conditions for which drugs that deliver 6-thioguanine are used, it is important to remember that the claims of the '623 and '302 patents only cover immune-mediated gastrointestinal diseases and non-IBD autoimmune disease, which have significantly different treatment protocols and clinical endpoints than other diseases such as treatment of leukemia and preventing rejection in organ transplant patients.

38. For both immune-mediated gastrointestinal disorders and non-IBD autoimmune diseases, azathioprine is presumed to work by suppressing an exaggerated immune response contributing to the disease pathogenesis.

[Rebuttal Expert Report of Brian W. Napper, filed Feb. 28, 2007]

[Caption omitted in printing]

* * *

24. * * * Mayo was prepared to charge a test fee of $193.50 and estimated the test cost at $77.40. These figures indicate that Mayo would expect an approximate 60% profit margin on the new test.

25. I have been provided with the history of Prometheus sales of the subject diagnostic tests to Mayo over the period 1999 through January 2007. As shown in the table below, Prometheus' average selling price ("ASP") of the subject diagnostic tests to Mayo was approximately $262.[26] Prometheus' subject diagnostic tests are priced, on average, approximately 25% higher than Mayo's proposed pricing, which all other variables held constant, is indicative of Prometheus' ability to charge a price premium on the subject diagnostic tests.

Total Charges	Total Orders	ASP
$4,606,370	17,552	$262

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[26] Exh. 383

[Declaration of Dr. Yves Théorêt in Support of Prometheus Laboratories Inc.'s Opposition to Defendants' Motion for Summary Judgment of Patent Invalidity Under 35 U.S.C. §101, filed Feb. 28, 2007]

[Caption omitted in printing]

* * *

5. To perform HPLC according to one method referenced in the patents-in-suit (sometimes referred to as the "Lennard" method because Dr. Lennard described it in articles), one would perform the following steps to a blood sample:

- Collect the blood in a tube with lithium heparin or sodium EDTA;
- Separate the red blood cells from the buffy coat and plasma (discarding the latter two);
- Suspend few times (clean-up) the red blood cells with a salt solution and quantify the red blood cell in the final solution;
- Transfer a certain amount of lysed red blood cell solution to a tube and add water, DTT and acid;
- Boil the solution;
- The 6-TG nucleotides and 6-MMP nucleotides (and 6-MMP itself) are broken down;
- An alkaline solution is added to the boiled solution;
- An organic solvent is added to help extract the components of interest;

- Shake and centrifuge the solution to separate the organic and aqueous layers;
- Add diluted hydrochloric acid;
- Shake and centrifuge again and discard the organic layer;
- Run some of the remaining acidic solution through a chromatograph connected to a detector and controlled by a specific software (a machine);
- The machine measures the amounts of analytes of interest by calculating on a chromatogram either peak height or peak area;
- The peak height or peak are is put into an equation which produces the metabolite concentrations in red blood cells.

[See, e.g., Exh. 3]. This is one method of performing HPLC and there are other HPLC methods that similarly alter and change the blood sample by adding solutions and extracting elements to determine the metabolite levels. *[See, e.g., Exh. 4, Exh. 1 at 9:12-40].*

6. There are several other methods described in the Patents besides HPLC for determining metabolite levels. *[Exh. 1 at 9:40-65; Exh. 5-8].* All alter and manipulate the blood or other tissue being tested to extract the metabolites and then determine the concentrations. Determining metabolite levels requires significant chemical and physical alteration of blood or human tissue. In other words, at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue.

7. All the methods I am aware of for determining metabolite levels involve alteration and manipula-

tion of the tissue being tested to measure metabolite concentrations. This is because metabolite levels are not detectable in raw human tissue. Significant chemical changes to the tissue are required.

* * *

[C. Cuffari, E.G. Seidman, S. Latour, and Y. Théorêt, *Quantitation of 6-thioguanine in peripheral blood leukocyte DNA in Crohn's disease patients on maintenance 6-mercaptopurine therapy*, 74 CAN. J. PHYSIOL. PHARMACOL. 580–585 (1996), filed Feb. 28, 2007]

* * *

INTRODUCTION

6-Mercaptopurine (6MP) and its precursor azathioprine are immunosuppressive drugs used in the treatment of recalcitrant inflammatory bowel disease (IBD) (O'Brien et al. 1991). They have been shown to eliminate the need for corticosteroids in about 75% of patients, with a mean response time of 3 months (O'Brien et al. 1991; Verhavo et al. 1990). Although employed for many years, their use in pediatrics has been restricted by concerns of cytotoxicity (Markowitz and Daum 1991; Present et al. 1989).

6MP and azathioprine are lymphocytotoxic, inhibiting nucleic acid metabolism in the sequence that follows antigen stimulation (Brogan et al. 1985). Their immunosuppressive properties are thought to be mediated by the active 6MP metabolite 6-thioguanine (6TG). The first step in 6MP metabolism is mediated by the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT), which converts

the parent drug to 6-thioinosine 5'-monophosphate. Subsequent biotransformation results in the formation of several metabolites, including 6-thioguanosine and 6-thiodeoxyguanosine nucleotides (Fig. 1) (Lennard 1992). Collectively, 6TG residues from these nucleotides are incorporated into DNA, inducing cytotoxibity and immunosuppression (Christie et al. 1986). * * *

[Deposition of Carmelo Cuffari, M.D., filed Mar. 9, 2007]

[Caption omitted in printing]

* * *

[Tr. 51] Q. Now, do you believe it to be the case that 250 is associated with a greater likelihood of disease remission in patients receiving azathioprine who have IBD?

* * *

Q. And I speak of 6-TG.

A. Yes.

Q. And do you believe that exists in the patient population today?

* * *

THE WITNESS: Yes.

Q. And it existed in 1996 as well?

* * *

THE WITNESS: Based on the 25 patients that we studied, yes.

* * *

[Declaration of Dr. Bruce Bostrom in Support of Defendants' Reply in Support of their Motion for Summary Judgment of Patent Invalidity Under 25 U.S.C. § 101, filed Mar. 9, 2007]

[Caption omitted in printing]

* * *

3. I am a Staff Pediatric Hematologist/Oncologist at Children's Hospitals & Clinics in Minneapolis, Minnesota. I am also an Associate Professor of Pediatrics at the University of Minnesota School of Medicine, and a Member of the University of Minnesota Cancer Center. I have more than twenty-five years of experience in treating cancer patients, and in doing medical research.

* * *

7. I am an author or co-author of more than 70 papers that have been published in peer-reviewed scientific or medical journals, and several book chapters. I have also authored or co-authored more than 100 abstracts. The principal area of my research, for the last 10-15 years, involves treatment of childhood leukemia, including development and evaluation of clinical trials as well as pilot studies for initial treatment and the treatment of relapse. I have also done research in pharmacokinetics: the measurement and interpreting of drug levels, for various drugs including: thiopurine metabolites in children with leukemia, busulfan in patients with cancer and blood disorders undergoing bone marrow transplantation, and other drugs (i.e. etoposide, cytarabine, daunomycin, fluconizole, liposomal interleukin-2). I have done research in clinical bone marrow transplantation for leukemia and childhood solid tumors

including pioneering the collection and use of peripheral blood stem cells for transplantation in children. I have done research in the treatment of childhood solid tumors including development of clinical trials and the use of animal models for the treatment of a childhood tumor neuroblastoma. I have also done research in the treatment of childhood hematologic diseases (aplastic anemia and immune thrombocytopenic purpura) and benign tumors (lymphangioma).

8. I have extensive research experience relating to the measurement and interpretation of thiopurine metabolites in childhood leukemia. In addition, I have participated in research relating to the measurement and interpretation of thiopurine metabolites in patients with Crohn's disease.

9. I began measuring thiopurine metabolites in the mid-1980s, after reviewing an article by Dr. Lynn Lennard entitled *Childhood Leukemia: A Relationship Between Intracellular 6-Mercaptopurine Metabolites and Neutropenia*, published in 1983 in the British Journal of Clinical Pharmacology. I began collaborating with Dr. Gary Erdmann on various projects to measure thiopurine metabolites in children with leukemia. At the time, Dr. Erdmann had developed an assay for measuring 6-TGN, and he was in the process of developing an assay to measure 6-MMP. Our initial work involved about 65 patients. In an initial pilot study, we described the typical ranges for both metabolites in children with leukemia on 6-MP therapy. As part of this initial pilot, we also measured 6-TGN and 6-MMP levels in five pediatric patients with Crohn's disease, in collaboration with Dr. Richard Stafford at Minneapolis Children's Medical Center (now Children's Hospitals and Clinics of Minnesota). We subsequently developed two clinical

trials through the Children's Cancer Group (now the Children's Oncology Group) involving the measurement of 6-TGN and 6-MMP levels in roughly 700 patients with childhood leukemia.

* * *

17. Once ingested, the drugs azathioprine (AZA) and 6-mercaptopurine (6-MP) are metabolized, in the body, into their active metabolites, which can be divided into two major groups: the 6-thioguanine nucleotide group (6-TGN) and 6-methylmercaptopurine group (6-MMP(N)). A person's ability to metabolize these drugs is genetically determined, and is regulated by her DNA. That ability exists in the body prior to ingesting the drug. Although the drugs AZA and 6-MP are man-made products, once they are ingested into the body, everything that happens from that point on is a natural process involving certain of the body's enzymes.

18. The '623 and '302 patents claim correlations between 6-TGN levels greater than "about 230" pmol per 8 x 10^8 red blood cells and a greater likelihood of response to therapy, and between 6-TGN levels greater than "about 400" pmol per 8 x 108 red blood cells, and "about 7000" 6-MMP and a greater likelihood of toxic side effects. A correlation is nothing more than a tendency of two variables to vary in a particular way that is not expected due to chance. In this instance, the correlations claimed are tendencies for 6-TGN and 6-MMP levels to vary in a particular way with respect to an increased likelihood of therapeutic response and toxicity. Those tendencies are natural phenomena that result from the body's natural process, and are the result of the natural relationships. For instance, there is a natural relationship in the body between 6-TGN levels and disease activity.

There is also a natural relationship in the body between 6-TG and 6-MMP levels and toxic side effects. To the extent the claimed correlations exist, they existed in the patients studied in the patents-in-suit before the inventors observed and analyzed their data to quantify them. To the extent the correlations exist, they will be found in any comparable population of a sufficient sample size.

19. It is not necessary for a correlation to be true for every single person in a sample size in order for the correlation to exist. To the extent they exist, the correlations identified above are natural phenomena that existed before they were discovered by the inventors, and regardless of whether those correlations hold true for every single patient.

* * *

[Deposition of Dr. Richard Bloomfeld, excerpts filed Mar. 9, 2007 and May 18, 2009]

[Caption omitted in printing]

* * *

[Tr. 178] Q. And then you say: As a result, it is your opinion that the subsequent sets of Derm study data provided by Mr. Kroll to the study investigators carried over his original warning that the therapeutic range is 235 to 400. Do you see that?

A. Yes, I do.

Q. Then you don't cite anything. You say thus, the Derm study used a level of 6TG, less than about 230?

A. Yes, I do say that.

Q. Is that the entire basis of your opinion that the less than about 230 limitation of the claim is met?

MR. HOSTETLER: Objections, vague, also lack of foundation.

A. I don't think I understand your question.

Q. Well, you opine that there's infringement of the Derm study?

A. Yes

Q. And you've opined that Mr. Kroll provided to Drs. O'Brien and el-Azhary his therapeutic range, true?

A. True.

[Tr. 179] Q. And then you say he provided no information that altered or contradicted his original comment when he provided to Dr. el-Azhary and Dr. O'Brien subsequent sets of data, true?

A. Yes. He provided therapeutic range, and then he never rescinded or said this doesn't count. So.

Q. And that's it, that's your entire basis for why the Derm study after the first provision that you claim occurred with Mr. Kroll and Dr. O'Brien and el-Azhary infringed?

MR. HOSTETLER: Objection, vague.

A. I think we looked at these warnings here, you know, that indicates a need, a therapeutic range, that was provided in the Derm study. That's the basis for my opinion that there was a therapeutic range that indicates a need or warning or what have you, that it's here in Exhibit 20 and Exhibit 22.

Q. I understand that, and that was with the first set of data that you claim that happened, true?

A. Yes, that's with the data that's here.

Q. That was the first set of data, according to you, true?

A. I don't see where I characterize something as the [Tr. 180] first set of data.

Q. In my opinion, paragraph 62, this element is literally found in the Derm study, because the first set of Derm study data provided by Mr. Kroll to Drs. El-Azhary and O'Brien stated that the therapeutic range for 6TG was 235 to 400?

A. Thank you. Yes, I do see that. I refer to this as the first set of Derm data with that therapeutic range.

Q. And how many samples are there in that first set of Derm data?

A. There are 21 samples in this set of data in Exhibit 22, and it looks like there are 25 sets of data in what's labeled Exhibit 21.

Q. Okay. Do you understand some of the data from Exhibit 21 to be the same as the Exhibit 22?

A. Yes. If you look at the what's labeled ACC number and the date, you see that there are some that appear to be in both.

Q. So there's an overlap between those two exhibits?

A. There does appear to be overlap between those two exhibits.

Q. And then, according to you, Mr. Kroll never provided his therapeutic range comment again in

[Tr. 181] the subsequent exhibits he sent to Drs. el-Azhary and O'Brien, is that true?

A. I don't think I say that he never provided it. I say he provided no information that altered or contradicted the therapeutic range that he had given.

Q. But he didn't repeat the therapeutic range comment in the later data, true?

A. I don't have written here in my opinion that he did not do it. I say that he provided no information that altered or contradicted this original therapeutic range. I don't recall offhand to say here under oath that he never said that therapeutic range again.

Q. Well, if he didn't, would it be your opinion that the Derm study nonetheless infringed because he didn't contradict it?

A. If he provided a therapeutic range, a warning that indicates a need, numbers on, you know, 20 something here, 20 something here, whatever overlap there were, then that satisfies that requirement and he infringed. Once he provided that therapeutic range, warning, indicates a need and didn't retract it, then those people would [Tr. 182] still have that therapeutic range, warning, that indicates a need, what have you, for future use. That's my opinion.

Q. So in your opinion, if Dr. el-Azhary resumed today measuring metabolites, having the lab at Mayo Clinic measure metabolites, and Mr. Kroll sent her the results, has she infringed the patent today because he sent her a comment once in March of 2004?

MR. HOSTETLER: Objection, incomplete hypothetical.

A. I have never said who infringed the patent and who did what steps. If —

Q. Doctor, if Dr. el-Azhary resumed the Derm study today and started measuring metabolite levels again, and got those measurements from Mr. Kroll, would that resumption of the Derm study infringe because she was given the therapeutic range comment by Mr. Kroll in March of 2004?

MR. HOSTETLER: I just want to raise an objection that, Mr. Singer, I'm sure inadvertently interrupted Dr. Bloomfeld.

MR. SINGER: Thank you, counsel.

MR. HOSTETLER: But if he can finish his [Tr. 183] testimony, that would be good, and then just incomplete hypothetical.

A. I looked at this Derm study as a whole. If the Derm study as a whole resumed, it would still infringe.

Q. Even today, based on a comment made almost three years ago?

MR. HOSTETLER: Objection, incomplete hypothetical. Go ahead.

A. Not based exclusively on that comment several years ago.

Q. What else is it based on?

A. I would look at evidence that Dr. el-Azhary is in possession of that warning therapeutic range, and whatever evidence I had to formulate an opinion of whether the study would infringe.

Q. So as far as you're concerned, that therapeutic range comment can apply to the Derm study, it could have gone on for ten years, is that true?

MR. HOSTETLER: Objection, incomplete hypothetical. Go ahead.

A. Studies started in one way and continues unchanged, then infringed at the beginning and nothing has changed, it would infringe in the [Tr. 184] middle, it would infringe near the end and it would infringe at the end. I don't think there's a time frame in days, months, years, where it's going to change to not infringe if nothing about the studies changed.

* * *

[Tr. 194] Q. And I want you to assume Mr. Kroll provided to Dr. el-Azhary his therapeutic range comment of 6TGN 235 to 400. Do we have that?

A. Yes, we do.

Q. Now, I want you to assume that Dr. el-Azhary gets that information and throws it in the garbage can. Do you believe there to be infringement because Mr. Kroll has provided the information?

MR. HOSTETLER: Objection to form, incomplete hypothetical.

A. In my understanding of all the segments of that question, it sounds, in my interpretation of what you are saying, that all those claims were met so that infringed.

So then any other assumptions after those, you know, claims are met doesn't change my opinion that it infringed.

I've heard, again, in my understanding of that question, I think I've heard all the claims, you know, were met, and then what she does with that results does not change my opinion that it infringes.

Q. So she could take the e-mail from Mr. Kroll and [Tr. 195] crumple it up and throw it away and the claim would be infringed, in your view?

MR. HOSTETLER: Objection to form, incomplete hypothetical. Go ahead.

A. In my view, if it meets all of those claims, then it infringes, and anything that happens afterwards, you know, when they've given the results and that therapeutic range or warning or indicates a need, it infringes, whether they—

Q. Sorry to interrupt. Go ahead.

A. Whether she crumples it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with after all of those claims are infringed, doesn't change it.

[Declaration of Dr. Yves Théorêt in Support of Prometheus Laboratories Inc.'s Brief Regarding *In re Comiskey* and *In re Nuijten* Pursuant to Court's October 15, 2007 Order, filed Nov. 9, 2007]

[Caption omitted in printing]

* * *

3. In my February 27th declaration, I described how one would determine metabolite levels using the method called high performance liquid chromatography, also called high pressure liquid chromatography (both "HPLC"). 2/27/07 Théorêt Decl. at ¶5. I described that HPLC requires the use of machines, such as a detector, a pump, and an injector, which allows the measurement of the amounts of analytes of interest. 2/27/07 Théorêt Decl. at ¶5. To be clear, me-

tabolite levels *cannot* be determined in human blood using HPLC without the use of machines.

4. I also described in my declaration that there are other similar methods of determining metabolite levels. 2/27/07 Théorêt Decl. at ¶6. Again, to be clear, all methods I am aware of for determining 6-TG and 6-MMP metabolite levels require the use of a machine. I am not aware of any method for determining metabolite levels that does not require the use of a machine.

* * *

IN THE SUPREME COURT OF THE UNITED STATES

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

No. 10-1150

June 20, 2011

The petition for writ of certiorari to the United States Court of Appeals for the Federal Circuit is granted.

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On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

JOINT APPENDIX – VOLUME 2

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US006355623B2

(12) **United States Patent**
Seidman et al.

(10) **Patent No.: US 6,355,623 B2**
(45) **Date of Patent: *Mar. 12, 2002**

(54) **METHOD OF TREATING IBD/CROHN'S DISEASE AND RELATED CONDITIONS WHEREIN DRUG METABOLITE LEVELS IN HOST BLOOD CELLS DETERMINE SUBSEQUENT DOSAGE**

(75) Inventors: **Ernest G. Seidman**, Côte St. Luc; Yves **Théorêt**, Montreal, both of (CA)

(73) Assignee: **Hopital-Sainte-Justine**, Montreal (CA)

(*) Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(51) **Int. Cl.**[7] **A61K 31/70**

(52) **U.S. Cl.** **514/45**; 514/47; 514/48; 514/262; 514/391; 514/395

(58) **Field of Search** 514/45, 47, 48, 514/262, 391, 395

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(57) **ABSTRACT**

The present invention provides a method of optimizing therapeutic efficacy and reducing toxicity associated with 6–mercaptopurine drug treatment of an immune–mediated gastrointestinal disorder such as inflammatory bowel disease. The method of the invention includes the step of determining the level of one or more 6–mercaptopurine metabolites in the patient having an immune–mediated gastrointestinal disorder.

54 Claims, 3 Drawing Sheets

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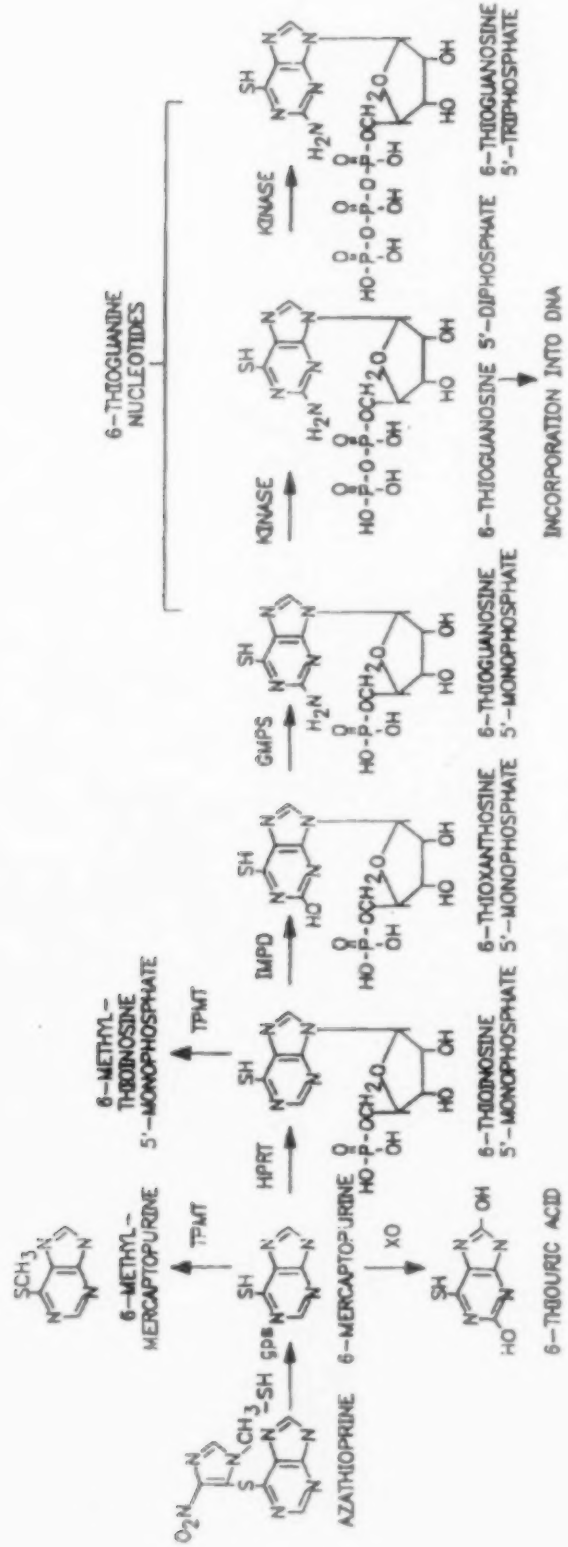
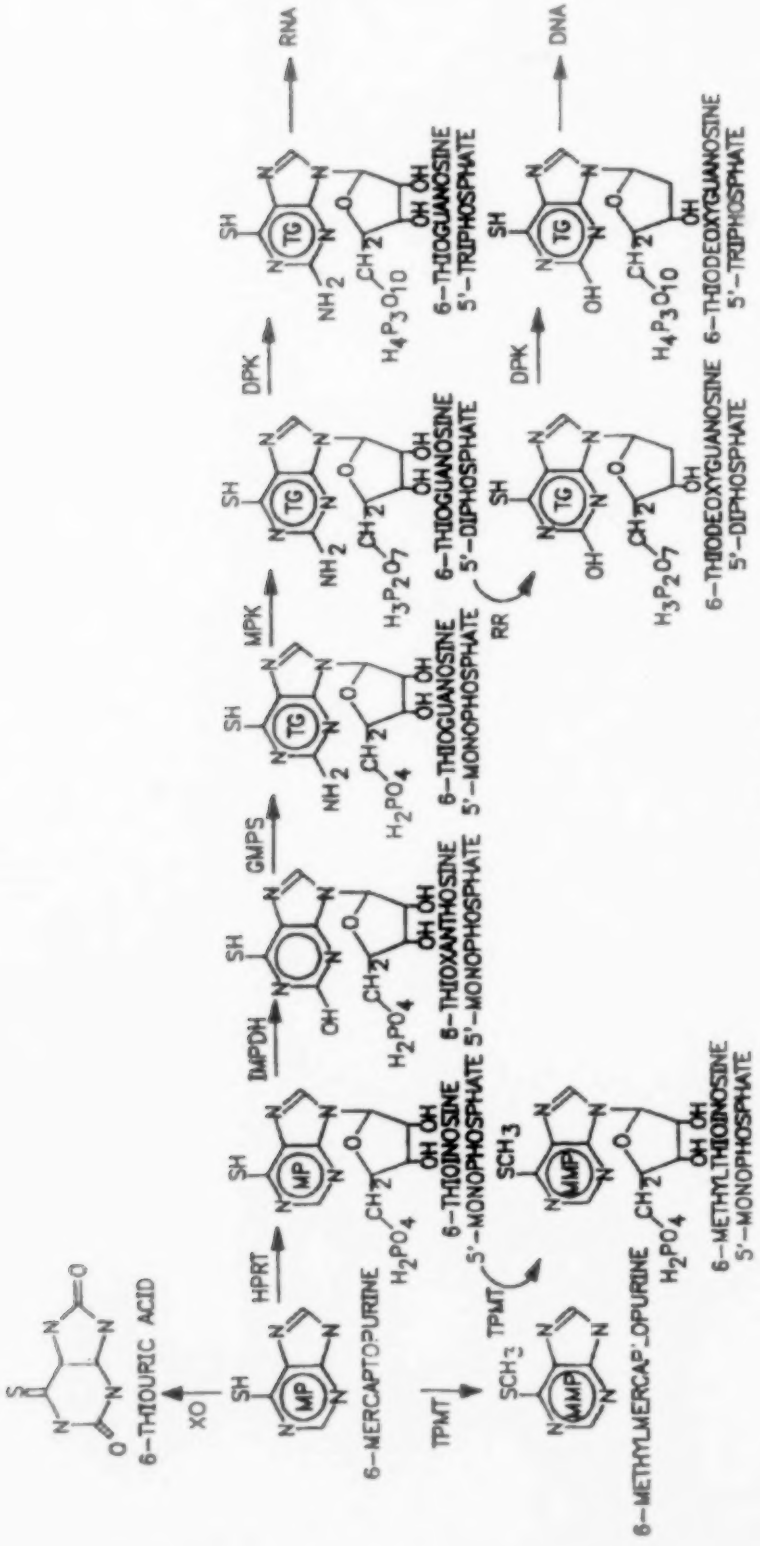

AZATHIOPRINE
6-MERCAPTOPURINE
6-THIOURIC ACID
6-METHYL-MERCAPTOPURINE
6-METHYL-THIOINOSINE 5'-MONOPHOSPHATE
6-THIOINOSINE 5'-MONOPHOSPHATE
6-THIOXANTHOSINE 5'-MONOPHOSPHATE
6-THIOGUANOSINE 5'-MONOPHOSPHATE
6-THIOGUANOSINE 5'-DIPHOSPHATE
6-THIOGUANOSINE 5'-TRIPHOSPHATE
6-THIOGUANOSINE NUCLEOTIDES
INCORPORATION INTO DNA
GPS
TPMT
HPRT
IMPD
GMPS
KINASE
XO

FIG. 1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TPMT
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TPMT
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GMPS
MPK
DPK
RR
DPK
6-THIOINOSINE 5'-MONOPHOSPHATE
6-THIOXANTHOSINE 5'-MONOPHOSPHATE
6-METHYLTHIOINOSINE 5'-MONOPHOSPHATE
6-THIOGUANOSINE 5'-MONOPHOSPHATE
6-THIOGUANOSINE 5'-DIPHOSPHATE
6-THIODEOXYGUANOSINE 5'-DIPHOSPHATE
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6-THIODEOXYGUANOSINE 5'-TRIPHOSPHATE
RNA
DNA

FIG. 2

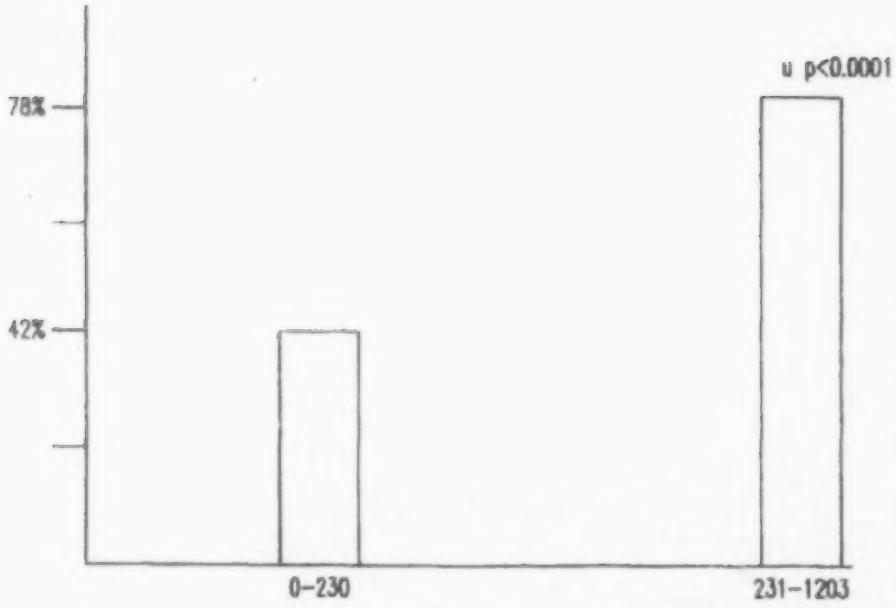

FIG. 3

METHOD OF TREATING IBD/CROHN'S DISEASE AND RELATED CONDITIONS WHEREIN DRUG METABOLITE LEVELS IN HOST BLOOD CELLS DETERMINE SUBSEQUENT DOSAGE

This application claims the benefit of priority of provisional application Ser. No. 60/101,714, filed Sep. 24, 1998, which is incorporated herein by reference now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates generally to autoimmunity and immune-mediated gastrointestinal disorders such as inflammatory bowel disease and more specifically to methods for optimizing treatment of immune-mediated gastrointestinal disorders.

BACKGROUND INFORMATION

Immune-mediated gastrointestinal disorders encompass a wide range of debilitating gastrointestinal diseases of various etiologies. One such immune-mediated gastrointestinal disorder, inflammatory bowel disease (IBD), is the collective term used to describe two gastrointestinal disorders of unknown etiology: Crohn's disease (CD) and ulcerative colitis (UC). The course and prognosis of IBD, which occurs world-wide and is reported to afflict as many as two million people, varies widely. Onset of IBD is predominantly in young adulthood with diarrhea, abdominal pain, and fever the three most common presenting symptoms. The diarrhea may range from mild to severe and in ulcerative colitis often is accompanied by bleeding. Anemia and weight loss are additional common signs of IBD. Ten percent to fifteen percent of all patients with IBD will require surgery over a ten year period. In addition, patients with IBD are at increased risk for the development of intestinal cancer. Reports of an increasing occurrence of psychological problems, including anxiety and depression, are perhaps not surprising symptoms of what is often a debilitating disease that strikes people in the prime of life.

6-Mercaptopurine (6-MP) and azathioprine (AZA), a prodrug that is non-enzymatically converted to 6-mercaptopurine (6-MP), are 6-MP drugs that can be used as an effective treatment for inflammatory bowel diseases such as Crohn's disease and ulcerative colitis (Kirschner *Gastroenterology* 115:813–821 (1998)). 6-MP can be enzymatically converted to various 6-MP metabolites, including 6-methyl-mercaptopurine (6-MMP) and 6-thioguanine (6-TG) and their nucleotides. 6-TG nucleotides are thought to be the active metabolite in mediating many of the effects of 6-MP drug treatment.

Thiopurine methyltransferase (TPMT) is a cytoplasmic enzyme that preferentially catalyzes the S-methylation of 6-MP and 6-TG to form S-methylated metabolites such as 6-MMP and 6-methylthioguanine (6-MTG), respectively. TPMT exhibits genetic polymorphism, with 89% of Caucasians and African Americans having high activity, 11% intermediate activity and 1 in 300 TPMT deficient. Clinical studies with AZA and 6-MP have shown an inverse relationship between TPMT activity and 6-TGN accumulation. Patients who less efficiently methylate these thiopurines have more extensive conversion to 6-TGN, which can lead to potentially fatal hematopoietic toxicity. Therefore, patients who have less active TPMT can be more susceptible to toxic side effects of 6-MP therapy.

Although drugs such as 6-MP and AZA have been used for treating IBD, non-responsiveness and drug toxicity

unfortunately complicate treatment in some patients. Complications associated with 6-MP drug treatment include allergic reactions, neoplasia, opportunistic infections, hepatitis, bone marrow suppression, and pancreatitis. Therefore, many physicians are reluctant to treat patients with AZA because of its potential side effects, especially infection and neoplasia.

Thus, there exists a need to develop methods to optimize the dose of 6-mercaptopurine drugs and assess biotransformation in individual patients to optimize the therapeutic efficacy of 6-mercaptopurine drugs while minimizing toxic side effects. The present invention satisfies this need and provides related advantages as well.

SUMMARY OF THE INVENTION

The present invention provides a method of optimizing therapeutic efficacy of 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder. The method includes the steps of administering a 6-mercaptopurine drug to a subject having an immune-mediated gastrointestinal disorder; and determining a level of 6-thioguanine in the subject having the immune-mediated gastrointestinal disorder, where a level of 6-thioguanine less than a level corresponding to about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to the subject and where a level of 6-thioguanine greater than a level corresponding to about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject. The methods are directed to treating immune-mediated gastrointestinal disorders, including inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease. In a method of optimizing therapeutic efficacy of 6-mercaptopurine treatment of IBD, the subject having IBD can be, for example, a pediatric subject. The level of 6-thioguanine can be determined, for example, in red blood cells using high pressure liquid chromatography.

The present invention also provides a method of reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder. The method of reducing toxicity associated with an immune-mediated gastrointestinal disorder includes the steps of administering a 6-mercaptopurine drug to a subject having the immune-mediated gastrointestinal disorder; and determining a level of a 6-mercaptopurine metabolite in the subject having the immune-mediated gastrointestinal disorder, where a level of the 6-mercaptopurine metabolite greater than a predetermined toxic level of the 6-mercaptopurine metabolite indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby reducing toxicity associated with 6-mercaptopurine drug treatment of the immune-mediated gastrointestinal disorder. In a method of the invention, the 6-mercaptopurine metabolite can be, for example, 6-thioguanine and the predetermined toxic level of 6-thioguanine can correspond, for example, to a level of about 400 pmol per $8x10^8$ red blood cells. Where the elevated 6-mercaptopurine metabolite is 6-thioguanine, the toxicity associated with 6-mercaptopurine treatment can be, for example, hematologic toxicity. The 6-mercaptopurine metabolite also can be a metabolite such as 6-methyl-mercaptopurine and the predetermined toxic level of 6-methyl-mercaptopurine can correspond, for example, to a level of about 7000 pmol per

8×10^8 red blood cells. Where the elevated 6-mercaptopurine metabolite is 6-methyl-mercaptopurine, the toxicity associated with 6-mercaptopurine treatment can be, for example, hepatic toxicity.

Further provided by the invention is a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder. The method includes the steps of administering a 6-mercaptopurine drug to a subject having an immune-mediated gastrointestinal disorder; determining a level of 6-thioguanine in the subject having the immune-mediated gastrointestinal disorder; and determining a level of 6-methyl-mercaptopurine in the subject having the immune-mediated gastrointestinal disorder, where a level of 6-thioguanine less than a predetermined minimal therapeutic level indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby increasing therapeutic efficacy; where a level of 6-thioguanine greater than a predetermined toxic level of 6-thioguanine indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby reducing toxicity associated with 6-mercaptopurine treatment of the immune-mediated gastrointestinal disorder; and where a level of 6-methyl-mercaptopurine greater than a predetermined toxic level of 6-methyl-mercaptopurine indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby reducing toxicity associated with 6-mercaptopurine treatment of the immune-mediated gastrointestinal disorder.

In such a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder, the predetermined minimal therapeutic level of 6-thioguanine can be, for example, a level corresponding to about 230 pmol per 8×10^8 red blood cells; the predetermined toxic level of 6-thioguanine can be, for example, a level corresponding to about 400 pmol per 8×10^8 red blood cells; and the predetermined toxic level of 6-methyl-mercaptopurine can be, for example, a level corresponding to about 7000 pmol per 8×10^8 red blood cells. The level of 6-thioguanine and 6-methyl-mercaptopurine each can be conveniently determined, for example, in red blood cells using high pressure liquid chromatography. The invention further provides methods to optimize the therapeutic efficacy of 6-mercaptopurine drug treatment of a non-IBD autoimmune disease.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mercaptopurine metabolism and the structures of 6-mercaptopurine (6-MP) metabolites. The initial metabolism of 6-MP is catalyzed by thiopurine methyltransferase (TPMT), xanthine oxidase (XO), and hypoxanthine phosphoribosyltransferase (HPRT). Further metabolism of the thionucleotide is catalyzed by inosine monophosphate dehydrogenase (IMPD) and guanosine monophosphate synthetase (GMPS). The breakdown of azathioprine to 6-mercaptopurine is nonenzymatic.

FIG. 2 shows 6-mercaptopurine (6-MP) metabolism and the 6-MP metabolites that are measured as 6-MP, 6-thioguanine (6-TG) and 6-methyl-mercaptopurine (6-MMP) (indicated as "MP," "TG" and "MMP" inside the base). 6-TG mono-phosphate is converted to the di- and tri-phosphate by monophosphate kinase (MPK) and diphosphate kinase (DPK), respectively. The ribonucleoside diphosphate is converted to deoxyribonucleoside diphosphate by ribonucleotide reductase (RR).

FIG. 3 shows ranges of 6-thioguanine in IBD patients treated with a 6-MP drug.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of optimizing therapeutic efficacy of 6-mercaptopurine (6-MP) drug treatment of an immune-mediated gastrointestinal disorder. The method includes the steps of administering a 6-MP drug to a subject having an immune-mediated gastrointestinal disorder; and determining a level of 6-thioguanine (6-TG) in the subject having the immune-mediated gastrointestinal disorder, where a level of 6-TG less than a level corresponding to about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of 6-MP drug subsequently administered to the subject and where a level of 6-TG greater than a level corresponding to about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject. The methods are directed to treating immune-mediated gastrointestinal disorders, including inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease. In a method of optimizing therapeutic efficacy of 6-MP treatment of IBD, the subject having IBD can be, for example, a pediatric subject. The level of 6-TG can be determined, for example, in red blood cells using high pressure liquid chromatography (HPLC).

The invention provides methods of optimizing therapeutic efficacy of 6-MP drug treatment of an immune-mediated gastrointestinal disorder. The methods of the invention are particularly useful for treating an immune-mediated gastrointestinal disorder such as IBD, including Crohn's disease and ulcerative colitis and subtypes thereof. The methods of the invention allow the clinician to provide an individually optimized dosage of a 6-MP drug so as to achieve a target level of a 6-MP metabolite in a particular patient having an immune-mediated gastrointestinal disorder, thereby optimizing the effectiveness of 6-MP drug therapy in the patient. The methods of the invention for optimizing therapeutic efficacy of 6-MP drug treatment involve determining the level of 6-TG in a patient having an immune-mediated gastrointestinal disorder. As disclosed herein, the level of 6-TG measured in a patient treated with a 6-MP drug was an indicator of the effectiveness of drug treatment. A level of at least 230 pmol 6-TG/8×10^8 red blood cells (RBC) was found in responders to drug therapy (see Examples I and II). These results indicate that determining the level of 6-TG can be used to assess whether a patient has a level of 6-TG that is sufficient to alleviate symptoms of an immune-mediated gastrointestinal disorder such as IBD, thus optimizing therapeutic efficacy.

As used herein, the term "6-mercaptopurine drug" or "6-MP drug" refers to any drug that can be metabolized to an active 6-mercaptopurine metabolite that has therapeutic efficacy such as 6-TG. Exemplary 6-mercaptopurine drugs as defined herein include 6-mercaptopurine (6-MP) and azathioprine (AZA). As illustrated in FIG. 1, both of 6-MP and AZA can be metabolized to 6-mercaptopurine metabolites such as the exemplary 6-mercaptopurine metabolites shown in FIG. 1, including 6-thioguanine (6-TG), 6-methyl-mercaptopurine (6-MMP) and 6-thiouric acid. (Lennard, *Eur. J. Clin. Pharmacol.* 43:329–339 (1992)).

Other 6-MP drugs include, for example, 6-methylmercaptopurine riboside and 6-TG (Loo et al., *Clin.*

Pharmacol. Ther. 9:180–194 (1968); O'Dwyer et al., *J. Natl. Cancer Inst.* 83:1235–1240 (1991); Erb et al., *Cancer Chemother. Pharmacol.* 42:266–272 (1998); Lancaster et al., *Br. J. Haematol.* 102:439–443 (1998); Ingle et al., *Am. J. Clin. Oncol.* 20:69–72 (1997); Evans and Relling, *Leuk. Res.* 18:811–814 (1994)). 6-TG is a particularly useful 6-MP drug in patients having high TPMT activity. Patients exhibiting high TPMT activity are expected to more easily convert 6-MP drugs such as 6-MP and AZA to 6-MMP (see FIGS. 1 and 2). As disclosed herein, high levels of 6-MMP are associated with hepatotoxicity (see Examples I and II). Therefore, patients with high TPMT activity can be more susceptible to toxic effects of 6-MP drug therapy. By administering 6-TG, which is an active 6-MP metabolite associated with therapeutic efficacy (see Examples I and II), the toxicity that can be associated with conversion of 6-MP to 6-MMP is bypassed.

It is understood that the 6-MP metabolites can be the metabolites shown in FIG. 1 or analogues thereof. As used herein, the term "6-thioguanine" or "6-TG" refers to 6-thioguanine or analogues thereof, including molecules having the same base structure, for example, 6-thioguanine ribonucleoside, 6-thioguanine ribonucleotide mono-, di- and tri-phosphate, 6-thioguanine deoxyribonucleoside and 6-thioguanine deoxyribonucleotide mono-, di, and triphosphate. The term "6-TG" also includes derivatives of 6-thioguanine, including chemical modifications of 6-TG, so long as the structure of the 6-TG base is preserved.

As used herein, the term "6-methyl-mercaptopurine" or "6-MMP" refers to 6-methyl-mercaptopurine or analogues thereof, including analogues having the same base structure, for example, 6-methyl-mercaptopurine ribonucleoside, 6-methyl-mercaptopurine ribonucleotide mono-, di-, and tri-phosphate, 6-methyl-mercaptopurine deoxyribonucleoside, and 6-methyl-mercaptopurine deoxyribonucleotide mono-, di- and tri-phosphate. The term "6-MMP" also includes derivatives of 6-methyl-mercaptopurine, including chemical modifications of 6-MMP, so long as the structure of the 6-MMP base is preserved.

The methods of the invention relate to treatment of an immune-mediated gastrointestinal disorder. As used herein, the term "immune-mediated gastrointestinal disorder" or "immune-mediated GI disorder" refers to a non-infectious disease of the gastrointestinal tract or bowel that is mediated by the immune system or cells of the immune system. Immune-mediated gastrointestinal disorders include, for example, inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

The methods of the invention are particularly useful for treating IBD, or subtypes thereof, which has been classified into the broad categories of Crohn's disease and ulcerative colitis. As used herein, "a subject having inflammatory bowel disease" is synonymous with the term "a subject diagnosed with having an inflammatory bowel disease," and means a patient having Crohn's disease or ulcerative colitis. Crohn's disease (regional enteritis) is a disease of chronic inflammation that can involve any part of the gastrointestinal tract. Commonly, the distal portion of the small intestine (ileum) and cecum are affected. In other cases, the disease is confined to the small intestine, colon or anorectal region. Crohn's disease occasionally involves the duodenum and stomach, and more rarely the esophagus and oral cavity.

The variable clinical manifestations of Crohn's disease are, in part, a result of the varying anatomic localization of the disease. The most frequent symptoms of CD are abdominal pain, diarrhea and recurrent fever. CD is commonly associated with intestinal obstruction or fistula, which is an abnormal passage between diseased loops of bowel, for example. Crohn's disease also includes complications such as inflammation of the eye, joints and skin; liver disease; kidney stones or amyloidosis. In addition, CD is associated with an increased risk of intestinal cancer.

Several features are characteristic of the pathology of Crohn's disease. The inflammation associated with CD, known as transmural inflammation, involves all layers of the bowel wall. Thickening and edema, for example, typically also appear throughout the bowel wall, with fibrosis also present in long-standing disease. The inflammation characteristic of CD also is discontinuous in that segments of inflamed tissue, known as "skip lesions," are separated by apparently normal intestine. Furthermore, linear ulcerations, edema, and inflammation of the intervening tissue lead to a "cobblestone" appearance of the intestinal mucosa, which is distinctive of CD.

A hallmark of Crohn's disease is the presence of discrete aggregations of inflammatory cells, known as granulomas, which are generally found in the submucosa. Some Crohn's disease cases display the typical discrete granulomas, while others show nonspecific transmural inflammation. As a result, the presence of discrete granulomas is indicative of CD, although the absence of granulomas also is consistent with the disease. Thus, transmural or discontinuous inflammation, rather than the presence of granulomas, is a preferred diagnostic indicator of Crohn's disease (Rubin and Farber, *Pathology* (Second Edition) Philadelphia: J. B. Lippincott Company (1994)).

Ulcerative colitis (UC) is a disease of the large intestine characterized by chronic diarrhea with cramping abdominal pain, rectal bleeding, and loose discharges of blood, pus and mucus. The manifestations of ulcerative colitis vary widely. A pattern of exacerbations and remissions typifies the clinical course of most UC patients (70%), although continuous symptoms without remission are present in some patients with UC. Local and systemic complications of UC include arthritis, eye inflammation such as uveitis, skin ulcers and liver disease. In addition, ulcerative colitis and especially long-standing, extensive disease is associated with an increased risk of colon carcinoma.

Several pathologic features characterize UC in distinction to other inflammatory bowel diseases. Ulcerative colitis is a diffuse disease that usually extends from the most distal part of the rectum for a variable distance proximally. The term left-sided colitis describes an inflammation that involves the distal portion of the colon, extending as far as the splenic flexure. Sparing of the rectum or involvement of the right side (proximal portion) of the colon alone is unusual in ulcerative colitis. The inflammatory process of ulcerative colitis is limited to the colon and does not involve, for example, the small intestine, stomach or esophagus. In addition, ulcerative colitis is distinguished by a superficial inflammation of the mucosa that generally spares the deeper layers of the bowel wall. Crypt abscesses, in which degenerated intestinal crypts are filled with neutrophils, also are typical of ulcerative colitis (Rubin and Farber, supra, 1994).

In comparison with Crohn's disease, which is a patchy disease with frequent sparing of the rectum, ulcerative colitis is characterized by a continuous inflammation of the colon that usually is more severe distally than proximally. The inflammation in ulcerative colitis is superficial in that it is usually limited to the mucosal layer and is characterized by

an acute inflammatory infiltrate with neutrophils and crypt abscesses. In contrast, Crohn's disease affects the entire thickness of the bowel wall with granulomas often, although not always, present. Disease that terminates at the ileocecal valve, or in the colon distal to it, is indicative of ulcerative colitis, while involvement of the terminal ileum, a cobblestone-like appearance, discrete ulcers or fistulas suggest Crohn's disease.

In addition to IBD, immune-mediated GI disorders also include other gastrointestinal diseases such as lymphocytic colitis; microscopic colitis; collagenous colitis; autoimmune enteropathy, including autoimmune enteritis and autoimmune enterocolitis; allergic gastrointestinal disease; and eosinophilic gastrointestinal disease, including eosinophilic gastroenteritis and eosinophilic enteropathy.

Over the past two decades, the histological evaluation of colorectal biopsies obtained by colonoscopy has expanded the spectrum of chronic IBD. A new group of immune-mediated bowel disorders has emerged, characterized by chronic watery diarrhea, minimal or absent endoscopic findings, and inflammatory changes in mucosal biopsies. Lymphocytic colitis, also commonly referred to as microscopic colitis, is a clinicopathological syndrome characterized primarily by lymphocytic infiltration of the epithelium. Collagenous colitis is defined by the presence of a collagenous band below the surface epithelium, accompanied by an increase in inflammatory cell infiltrate (Lazenby et al. *Hum. Pathol.* 20:18–28 (1989)). These disorders are often associated with other autoimmune diseases such as rheumatoid arthritis, pernicious anemia, thyroiditis, uveitis and type I diabetes mellitus. Clinicians have used immunosuppressive drugs, including 6-MP, to treat these disorders (Dealandres et al. *J. Pediatr. Gastroenterol. Nutr.* 25:341–346 (1997)).

Autoimmune enteropathy, including autoimmune enteritis and autoimmune enterocolitis, is a syndrome of severe secretory diarrhea and marked enterocolitis, in association with diagnostic circulating antibodies to enterocytes (Seidman et al., *J. Pediatr.* 117:929–932 (1990)). This syndrome, most often seen in infancy, can be seen in association with other autoimmune diseases. Complete villous atrophy is associated with a severe inflammatory reaction on small bowel biopsies. Although some cases remit after an extended period of time, most patients die without immunosuppressive therapy, which can include 6-MP drug therapy.

Eosinophilic gastrointestinal disease, including eosinophilic gastroenteritis and eosinophilic enteropathy, is characterized by a dense infiltration of eosinophils in one or more areas of the gastrointestinal tract, variable intestinal symptoms, and usually a peripheral eosinophilia (80% of cases). Food allergic, including allergic gastrointestinal disease, and eosinophilic disorders of the gastrointestinal tract are commonly treated by dietary elimination of the offending nutrients. However, both food induced and eosinophilic enteropathies may, in certain circumstances, require corticosteroid and immunosuppressive therapy, including 6-MP (Russo et al., *Pediatric Dev. Path.* 2:65–71 (1999)).

The methods of the invention relate to optimizing therapeutic efficacy of 6-MP drug treatment of an immune-mediated GI disorder, including IBD such as Crohn's disease and ulcerative colitis and subtypes thereof. The methods of the invention are particularly useful for treating patients dependent on steroid therapy, for maintenance of remission of disease in Crohn's disease and ulcerative colitis patients. As used herein, the phrase "optimizing therapeutic efficacy of 6-MP drug treatment" refers to adjusting the therapeutic dosage of a 6-MP drug such as 6-MP or azathioprine so that the concentration of a 6-MP metabolite that is correlated with effective treatment is maintained. As set forth above, the methods of the invention allow the clinician to provide an individually optimized dosage of a 6-MP drug so as to achieve a target level of a 6-MP metabolite in a particular patient, thereby optimizing the effectiveness of 6-MP drug therapy in the patient. Therapeutic efficacy generally is indicated by alleviation of one or more signs or symptoms associated with the disease. In the case of immune-mediated GI disorders, in particular IBD, therapeutic efficacy is indicated by alleviation of one or more signs or symptoms associated with the disease, including, for example, joint pain, arthritis, arthalgia, anorexia, growth failure, fistula closure, abdominal pain, diarrhea, recurrent fever, anemia, weight loss, rectal bleeding, inflammation of the intestine, and loose discharges of blood, pus and mucus. Methods for determining therapeutic efficacy, in particular for treating IBD, are disclosed herein in Examples I and II.

Therapeutic efficacy can be readily determined by one skilled in the art as the alleviation of one or more signs or symptoms of the disease being treated. In the case of IBD, patients can be analyzed using a Crohn's disease activity index (Best et al., *Gastroenterology* 70:439–444 (1976)). IBD patients can also be analyzed using a Harvey-Bradshaw index (HBI) (Harvey and Bradshaw, *Lancet* 1:514 (1980)). The Harvey-Bradshaw index provides an analytical method for measuring signs or symptoms of Crohn's disease, including the signs or symptoms of general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and complications such as arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula and abscess. The Harvey-Bradshaw index is particularly useful when evaluating pediatric patients.

Previous studies suggested that measurement of 6-MP metabolite levels can be used to predict clinical efficacy and tolerance to azathioprine or 6-MP (Cuffari et al., *Gut* 39:401–406 (1996a)). However, it was unknown what concentrations of 6-MP metabolites correlated with optimized therapeutic efficacy or with toxicity (Cuffari et al., supra, 1996a). As disclosed herein, levels of 6-MP metabolites such as 6-TG and 6-MMP were determined and correlated with therapeutic efficacy and toxicity associated with 6-MP drug therapy (see Examples I and II).

The invention is directed to methods of optimizing therapeutic efficacy of 6-MP drug treatment of an immune-mediated GI disorder by monitoring predetermined levels associated with therapeutic efficacy or toxicity and adjusting the 6-MP drug dosage so as to maintain an optimized dose that is efficacious and has reduced toxicity. The methods involve administering a 6-MP drug such as 6-MP or azathioprine to a subject having an immune-mediated GI disorder and determining a level of a 6-MP metabolite in the subject having the immune-mediated GI disorder. The methods of the invention are advantageous in that the dosage of a 6-MP drug can be adjusted to maximize the efficacy of treating an immune-mediated GI disorder such as IBD while minimizing toxicity associated with 6-MP drug treatment.

As used herein, the term "6-mercaptopurine metabolite" refers to a product derived from 6-mercaptopurine in a biological system. Exemplary 6-mercaptopurine metabolites are shown in FIG. 1 and include 6-thioguanine (6-TG), 6-methyl-mercaptopurine (6-MMP) and 6-thiouric acid and analogues thereof. For example, 6-MP metabolites include 6-TG bases such as 6-TG, 6-thioguanosine mono-, di- and

tri-phosphate; 6-MMP bases such as 6-methyl-mercaptopurine and 6-methyl-thioinosine monophosphate; 6-thioxanthosine (6-TX) bases such as 6-thioxanthosine mono-phosphate; 6-thioruric acid (6-TUA); and 6-MP bases such as 6-mercaptopurine and 6-thioinosine monophosphate (see FIG. 2). The immunosuppressive properties of 6-MP are believed to be mediated via the intracellular transformation of 6-MP to its active metabolites such as 6-TG and 6-MMP nucleotides. Furthermore, 6-MP metabolites such as 6-TG and 6-MMP were found to correlate with therapeutic efficacy and toxicity associated with 6-MP drug treatment of IBD patients (see Examples I and II).

The level of a 6-MP metabolite can be determined by methods well known in the art including, for example, those described in Lilleyman and Lennard, *Lancet* 343:1188–1190 (1994); Lennard and Singleton, *J. Chromatography Biomed. Applicat.* 583:83–90 (1992); Lennard and Singleton, *J. Chromatography* 661:25–33 (1994); and Cuffari et al., *Can. J. Physiol. Pharmacol.* 74:580–585 (1996b)). 6-MP metabolites such as 6-TG and 6-MMP can be measured, for example, by collecting red blood cells and extracting thiobases, for example, 6-MP, 6-TG, 6-TX and 6-MMP, which are released by acid hydrolysis. 6-MMP is converted to a form extractable by phenyl mercury salts (Dervieux and Boulieu, *Clin. Chem.* 44:2511–2525 (1998); Duchesne et al., *Proc. Amer. Soc. Clin. Oncol.* 13:137 (1994a); Duchesne et al., *Can. J. Physiol. Pharmacol.* 72:197 (1994b)). Such an analysis measures the thiobase and its analogues, including ribonucloside, ribonucleotide, deoxyribonucleoside, deoxyribonucleotide thiobases as well as mono-, di- and tri-phosphate analogues, which have been converted to thiobases.

Acid hydrolyzed extracts can be analyzed by resolving 6-MP metabolites and measuring their levels. For example, HPLC such as reverse phase HPLC is a useful method for resolving and measuring the levels of 6-MP metabolites, including 6-MP, 6-TG and 6-MMP (Lennard and Singleton, supra, 1992). Ultraviolet light (UV) detection can be used to measure the 6-MP metabolites. A particularly useful method of measuring 6-MP metabolites is isocratic reverse phase HPLC with UV detection (Cuffari et al., supra, 1996b).

Other methods for measuring 6-MP metabolites can also be used. For example, ion-pairing HPLC with dual UV-wavelength detection can be used to measure 6-MP metabolites (Zimm and Strong, *Anal. Biochem.* 160:1–6 (1987)). Additional methods for measuring 6-MP metabolites include, for example, capillary electrophoresis with laser-induced fluorescence detection (Rabel et al., *Anal. Biochem.* 224:315–322 (1995)); anion exchange chromatography and fluorescent detection (Tidd and Dedhar *J. Chromatography* 145:237–246 (1978)); lanthanum precipitation, acid hydrolysis, back extraction and fluorometric assay (Fletcher and Maddocks, *Brit. J. Clin. Pharmacol.* 10:287–292 (1980)); thin layer chromatography (Bennet and Allen, *Cancer Res.* 31:152–158 (1971)); precolumn derivatization with the thiol-reactive fluorophore monobromobimane, treatment with alkaline phosphatase, HPLC resolution and quantification by fluorometry (Warren and Slordal, *Anal. Biochem.* 215:278–283 (1993)); and enzymatic hydrolysis followed by HPLC separation and UV detection (Giverhaug et al., *Ther. Drug Monit.* 19:663–668 (1997)). 6-MP metabolites such as 6-TG can also be measured in DNA by degrading DNA to deoxyribonucleosides, derivatizing deoxy-6-TG with a fluorophore and resolving on reverse phase HPLC (Warren et al., *Cancer Res.* 55:1670–1674 (1995)).

As used herein, the level of a 6-MP metabolite can include the 6-MP metabolite itself, or the level of the 6-MP metabolite and analogues thereof. For example, as described above, acid hydrolysis can be used to release thionucleotides from a sample, resulting in conversion of mono-, di- and tri-phosphates to thiobases. In such an analysis, the level of several analogues of a thionucleotide are measured (see FIG. 2). For example, measuring 6-TG can include 6-thioguanosine 5'-mono-, di-, and tri-phosphate, and 6-thiodeoxyguanosine 5'-di-, and tri-phosphate. Measuring 6-MP can include 6-mercaptopurine and 6-thioinosine 5'-monophosphate. Measuring 6-MMP can include 6-methylmercaptopurine and 6-methylthioinosine 5'-monophosphate, and can also include 6-methylthioinosine di- and tri-phosphate, as well as 6-methyl thioguanosine.

A particularly useful determination of the level of a 6-MP metabolite is the median level of the 6-MP metabolite since the distribution of 6-MP metabolite values is trimodal. Unless otherwise designated, the levels referred to herein are median levels. A 6-MP metabolite level can also be a mean level, if so desired. Unless otherwise designated, the levels of 6-MP metabolites referred to herein are values per 8×10^8 RBC, whether reported as mean or median values.

6-MP metabolite levels can be conveniently assayed using red blood cells because such cells are readily available from the patient, lack a nucleus and are easy to manipulate. However, it should be understood that any measurement that allows determination of 6-MP metabolite levels can be used. For example, leukocytes can be used to measure 6-MP metabolite levels, which can be correlated with 6-MP metabolite levels in erythrocytes (Cuffari et al., supra, 1996b). Regardless of the method employed to measure 6-MP metabolites, one skilled in the art can readily measure 6-MP metabolite levels in a sample, for example, in leukocytes or DNA obtained from a patient, and correlate the level of 6-MP metabolites to the values disclosed herein, which were determined using RBC.

For convenience, levels of 6-MP metabolites disclosed herein are given in terms of an assay with RBC and, therefore, are given as an amount of a 6-MP metabolite in a given number of RBCs. 6-MP metabolites assayed in RBCs can also be determined relative to the amount of hemoglobin. However, it should be understood that one skilled in the art can measure 6-MP metabolite levels in samples other than RBCs and readily correlate such levels with 6-MP metabolite levels in RBCs. For example, one skilled in the art can readily determine levels of a 6-MP metabolite in cells such as leukocytes, or cells from the oral mucosa, and in RBCs by measuring the level of 6-MP metabolites in both types of cells and determining the correspondence between levels of 6-MP metabolites in RBCs and the levels in the other cells. Once a correspondence between 6-MP metabolites in RBCs and in a sample has been determined, one skilled in the art can use that correspondence to measure levels in the other sample and correlate those levels with the levels in RBCs disclosed herein.

As disclosed herein, the level of 6-TG in an IBD patient treated with a 6-MP drug was found to correlate with therapeutic efficacy (see Examples I and II). In particular, a median level of 230 pmol 6-TG/8×10^8 RBC or more was found in IBD patients who responded to 6-MP drug therapy. Thus, as disclosed herein, a level of at least about 230 pmol 6-TG per 8×10^8 RBC can be a minimal therapeutic level of 6-TG for efficaciously treating a patient. Accordingly, a level of 6-TG below about 230 pmol/8×10^8 RBC indicates a need to increase the amount of a 6-MP drug administered to the patient. A minimal therapeutic level of 6-TG for efficaciously treating a patient also can be, for example, at least

about 240 pmol per $8x10^8$ RBC; at least about 250 pmol per $8x10^8$ RBC; at least about 260 pmol per $8x10^8$ RBC; at least about 280 mol per $8x10^8$ RBC or at least about 300 pmol per $8x10^8$ RBC. It is understood that the minimal therapeutic levels of 6-TG disclosed herein are useful for treating immune-mediated gastrointestinal disorders, including IBD, as well as non-IBD autoimmune diseases.

The methods of the invention directed to determining whether a patient has a minimal therapeutic level of a 6-MP metabolite are useful for indicating to the clinician a need to monitor a patient for therapeutic efficacy and to adjust the 6-MP drug dose, as desired. For example, in a patient having less than a minimal therapeutic level of a 6-MP metabolite such as 6-TG and who also presents as unresponsive to 6-MP drug therapy or having poor responsiveness to 6-MP drug therapy as measured by minimal or no effect on a sign or symptom of the disease being treated, one skilled in the art can determine that the dosage of a 6-MP drug should be increased. However, if it is determined that a patient has less than a predetermined minimal therapeutic level of a 6-MP metabolite but is responsive to 6-MP therapy, the current dose of 6-MP drug can be maintained. Based on measuring 6-MP metabolite levels and assessing the responsiveness of the patient to 6-MP therapy, one skilled in the art can determine whether a 6-MP drug dose should be maintained, increased, or decreased.

Although 6-MP drugs such as 6-MP and azathioprine can be used for effective treatment of an immune-mediated GI disorder, including IBDs such as Crohn's disease or ulcerative colitis, administration of such drugs can be associated with toxic side effects. Toxicities associated with 6-MP drug administration include pancreatitis, bone marrow depression, allergic reactions and drug hepatitis as well as neoplasms and infectious complications (Present et al., *Annals Int. Med.* 111:641–649 (1989); Cuffari et al., supra, 1996a). As disclosed herein, various toxicities associated with 6-MP drug treatment, including hepatic toxicity, pancreatic toxicity and hematologic toxicity, correlate with the level of 6-MP metabolites in a subject administered a 6-MP drug (see Examples I and II).

Thus, the present invention also provides a method of reducing toxicity associated with 6-MP drug treatment of an immune-mediated GI disorder. The method of the invention for reducing toxicity associated with 6-MP drug treatment includes the steps of administering a 6-MP drug to a subject having an immune-mediated GI disorder; and determining a level of a 6-MP metabolite in the subject having the immune-mediated GI disorder, where a level of the 6-MP metabolite greater than a predetermined toxic level of the 6-MP metabolite indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP drug treatment of the immune-mediated GI disorder. In a method of the invention, the 6-MP metabolite can be, for example, 6-TG and the predetermined toxic level of 6-TG can correspond, for example, to a level of about 400 pmol per $8x10^8$ red blood cells. Where the elevated 6-MP metabolite is 6-TG, the toxicity associated with 6-MP treatment can be, for example, hematologic toxicity, including leukopenia or bone marrow suppression. The 6-MP metabolite also can be a metabolite such as 6-MMP, and the predetermined toxic level of 6-MMP can correspond, for example, to a level of about 7000 pmol per $8x10^8$ red blood cells. Where the elevated 6-MP metabolite is 6-MMP, the toxicity associated with 6-MP drug treatment can be, for example, hepatic toxicity.

As disclosed herein, the level of a 6-MP metabolite can be determined in a subject treated with a 6-MP drug and compared to a predetermined toxic level of a 6-MP metabolite such as 6-TG or 6-MMP to adjust future 6-MP drug administration, thereby reducing toxicity in the subject. For example, as disclosed herein, levels of 6-TG above about 400 pmol/$8x10^8$ RBC indicated that a patient was likely to experience toxicity, in particular hematologic toxicity such as leukopenia (see Examples I and II). Accordingly, a level of 6-TG above about 400 pmol/$8x10^8$ RBC can be a predetermined toxic level of 6-TG, which indicates that the amount of 6-MP drug subsequently administered should be decreased.

It is understood that, when a patient is determined to have a level of a 6-MP metabolite such as 6-TG or 6-MMP higher than a predetermined toxic level, one skilled in the art can make a determination as to whether a 6-MP drug dose should be decreased. For example, if the level of a 6-MP metabolite such as 6-TG or 6-MMP is higher than a predetermined toxic level, one skilled in the art can monitor for toxic side effects by measuring one or more of the toxicities associated with 6-MP drug treatment, as disclosed herein. As disclosed herein, a level of 6-TG greater than about 400 pmol per $8x10^8$ RBCs was associated with increased risk of leukopenia or bone marrow suppression. Therefore, one skilled in the art can measure white blood cells (WBC) in a patient having levels of 6-TG higher than a predetermined toxic level to determine if the patient is exhibiting signs of reduced WBC counts. If such a patient exhibits signs of leukopenia or bone marrow suppression, the 6-MP drug dose can be reduced. However, if it is determined that a patient has levels of a 6-MP metabolite higher than a predetermined toxic level but does not exhibit signs of leukopenia or other 6-MP drug toxicities, one skilled in the art can determine that the current 6-MP drug dose can be maintained. Based on measuring 6-MP metabolite levels and determining signs or symptoms of toxicities associated with 6-MP drug treatment, one skilled in the art can determine whether a 6-MP drug dose should be maintained or decreased. As such, a level of a 6-MP metabolite higher than a predetermined toxic level can indicate a need to measure a toxicity associated with 6-MP drug treatment such as measuring WBCs or any of the other signs or symptoms of toxicities associated with 6-MP drug treatment to determine if the 6-MP drug dose should be adjusted.

Furthermore, it is understood that, when decreasing the 6-MP drug dose, one skilled in the art will know or can readily determine whether the 6-MP drug dose should be decreased to a lower dose or whether 6-MP drug administration should be stopped for some period of time, or terminated. For example, if the clinician determines that 6-MP drug therapy should be stopped for some period of time due to levels of a 6-MP metabolite exceeding a level predetermined to be toxic, the levels of 6-MP metabolites can be monitored after stopping 6-MP drug therapy until the level of the toxic 6-MP metabolite returns to a safe, non-toxic level. At that time, the clinician can resume 6-MP drug therapy, if desired.

The methods of the invention for reducing toxicity associated with 6-MP drug treatment of a disease involve comparing a level of a 6-MP metabolite to a predetermined toxic level of a 6-MP metabolite. In general, a "predetermined toxic level" of a 6-MP metabolite means a level of a 6-MP metabolite that has been correlated with one or more toxicities associated with 6-MP drug treatment. As disclosed herein, a predetermined toxic level of 6-TG can be about 400 pmol per $8x10^8$ RBC. A predetermined toxic level of 6-TG also can be about 350 pmol per $8x10^8$ RBC; 370 pmol per $8x10^8$ RBC; 390 pmol per $8x10^8$ RBC; 425 pmol per $8x10^8$

RBC; or 450 pmol per 8x10RBC. It is understood that the predetermined toxic levels of 6-TG disclosed herein are useful for treating immune-mediated GI disorders, including IBD, as well as non-IBD autoimmune diseases.

Another 6-MP metabolite useful for predicting the likelihood of toxicity is 6-methyl-mercaptopurine (6-MMP). As disclosed herein, a level of greater than about 7000 pmol 6-MMP/$8x10^8$ in patients administered a 6-MP drug was associated with toxicity, in particular hepatotoxicity (see Examples I and II). These results indicate that the level of 6-MMP can be used to predict toxicity in a patient treated with a 6-MP drug. As disclosed herein, a predetermined toxic level of 6-MMP can be about 7000 pmol per $8x10^8$ RBC. A predetermined toxic level of 6-MMP also can be about 6000 pmol per $8x10^8$ RBC; 6500 pmol per $8x10^8$ RBC; 7500 pmol per $8x10^8$ RBC; or 8000 pmol per $8x10^8$ RBC. It is understood that the predetermined toxic levels of 6-MMP disclosed herein are useful for treating immune-mediated GI disorders, including IBD, as well as non-IBD autoimmune diseases. According to a method of the invention, if the level of 6-MMP is above a predetermined toxic level, the subsequent administration of a 6-MP drug can be decreased to minimize toxicity.

Further provided by the invention is a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-MP drug treatment of an immune-mediated GI disorder such as IBD. The method includes the steps of administering a 6-MP drug to a subject having an immune-mediated GI disorder; determining a level of 6-TG in the subject having the immune-mediated GI disorder; and determining a level of 6-MMP in the subject having the immune-mediated GI disorder, where a level of 6-TG less than a predetermined minimal therapeutic level indicates a need to increase the amount of 6-MP drug subsequently administered to the subject, thereby increasing therapeutic efficacy; where a level of 6-TG greater than a predetermined toxic level of 6-TG indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP treatment of the immune-mediated GI disorder; and where a level of 6-MMP greater than a predetermined toxic level of 6-MMP indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP drug treatment of the immune-mediated GI disorder.

In such a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-MP drug treatment of an immune-mediated GI disorder such as IBD, the predetermined minimal therapeutic level of 6-TG can be, for example, a level corresponding to about 230 pmol per $8x10^8$ red blood cells; the predetermined toxic level of 6-TG can be, for example, a level corresponding to about 400 pmol per $8x10^8$ red blood cells; and the predetermined toxic level of 6-MMP can be, for example, a level corresponding to about 7000 pmol per $8x10^8$ red blood cells. In a method of the invention, the subject having an immune-mediated GI disorder such as IBD can be, for example, a pediatric subject. The level of 6-TG and 6-MMP each can be conveniently determined, for example, in red blood cells using HPLC.

The methods of the invention are useful for optimizing the amount of a 6-MP drug to be administered to a patient with an immune-mediated GI disorder such as IBD. By measuring the levels of 6-MP metabolites such as 6-MMP and 6-TG, one skilled in the art can determine the 6-MP drug dosage that will result in optimized therapeutic efficacy and reduced toxicity when administered to a patient.

As disclosed herein, gender and age differences were observed in pediatric patients treated with 6-MP drug therapy (see Example III). Very little change in 6-MP metabolite levels of 6-TG and 6-MMP was seen for girls who had gone through puberty (older than age 12). However, boys who had gone through puberty (older than age 14) had a marked decrease in the level of 6-MMP, suggesting that hormonal changes occurring during puberty can affect the metabolism of a 6-MP drug. Therefore, the methods of the invention can additionally be used to monitor 6-MP metabolite levels in adolescents, particularly those going through puberty, in order to optimize therapeutic efficacy or minimize toxic side effects associated with 6-MP therapy.

As disclosed herein, TPMT genotyping is useful for predicting the effectiveness of 6-MP therapy in an IBD patient (see Example IV). Heterozygote patients are expected to have lower TPMT activity and should therefore be monitored for high levels of 6-TG for possible toxic levels associated with leukopenia or bone marrow suppression. 6-MP drug doses can be reduced accordingly. Wild type homozygous patients are expected to have higher TPMT activity and should therefore be monitored to maintain an effective therapeutic level of 6-TG and to determine if patients develop toxic levels of 6-MMP. Homozygous patients deficient in TPMT activity can be treated with lower doses of a 6-MP drug provided that patients are closely monitored for toxicity such as leukopenia. Therefore, TPMT genotyping can be used to predict patient responsiveness to and potential toxicities associated with 6-MP drug therapy. Furthermore, TPMT genotyping can be combined with other methods of the invention to both determine TPMT genotype and to monitor 6-MP metabolites. TPMT genotyping can be particularly valuable when determining a starting dose of 6-MP drug therapy but can also be useful when adjusting 6-MP drug doses after therapy has begun.

The invention additionally provides a method of optimizing therapeutic efficacy of 6-MP drug treatment of a non-IBD autoimmune disease. The method includes the steps of administering a 6-MP drug to a subject having a non-IBD autoimmune disease; and determining a level of 6-thioguanine (6-TG) in the subject having the non-IBD autoimmune disease, where a level of 6-TG less than a minimal therapeutic level indicates a need to increase the amount of 6-MP drug subsequently administered to the subject and where a level of 6-TG greater than a predetermined toxic level indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject. The level of 6-MMP can also be monitored in a patient having a non-IBD autoimmune disease to determine if the level is higher than a predetermined toxic level of 6-MMP.

The methods of the invention can be used to optimize therapeutic efficacy of 6-MP drug treatment of a non-IBD autoimmune disease. Such a non-IBD autoimmune disease can be any non-IBD autoimmune disease treatable by a 6-MP drug such as 6-MP or azathioprine and, in particular, can be a disease such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune hepatitis (chronic active hepatitis) or pemphigus vulgaris.

As used herein, the term "non-IBD autoimmune disease" means a disease resulting from an immune response against a self tissue or tissue component, including both self antibody responses and cell-mediated responses. The term non-IBD autoimmune disease encompasses organ-specific non-IBD autoimmune diseases, in which an autoimmune response is directed against a single tissue, including myasthenia gravis, vitiligo, Graves' disease, Hashimoto's disease, Addison's disease, autoimmune gastritis, and Type I diabetes mellitus. The term non-IBD autoimmune disease

also encompasses non-organ specific autoimmune diseases, in which an autoimmune response is directed against a component present in several or many organs throughout the body. Non-organ specific autoimmune diseases include, for example, systemic lupus erythematosus, progressive systemic sclerosis and variants, polymyositis and dermatomyositis, and rheumatoid disease. Additional non-IBD autoimmune diseases include pernicious anemia, primary biliary cirrhosis, autoimmune thrombocytopenia, and Sjögren's syndrome. One skilled in the art understands that the methods of the invention can be applied to these or other non-IBD autoimmune diseases treatable by a 6-MP drug such as 6-MP or azathioprine, or other 6-MP drugs, as desired. Specifically excluded from the term "non-IBD autoimmune disease" are diseases resulting from a graft versus host response and inflammatory bowel diseases such as Crohn's disease or ulcerative colitis.

The methods of the invention are also useful for treating a non-immune-mediated GI disorder autoimmune disease. As used herein, the term "non-immune-mediated GI disorder autoimmune disease" is a non-IBD autoimmune disease and specifically excludes immune-mediated GI disorders.

The methods of the invention can be particularly useful for optimizing therapeutic efficacy of 6-MP drug treatment of rheumatoid arthritis. Rheumatoid arthritis is a chronic systemic disease primarily of the joints, usually polyarticular, marked by inflammatory changes in the synovial membranes and articular structures and by muscle atrophy and rarefaction of the bones.

The methods of the invention also can be particularly valuable for optimizing therapeutic efficacy of 6-MP drug treatment of lupus erythematosus and, in particular, systemic lupus erythematosus (SLE). Systemic lupus erythematosus is a chronic, remitting, relapsing inflammatory, and sometimes febrile multisystemic disorder of connective tissue. SLE can be acute or insidious at onset and is characterized principally by involvement of the skin, joints, kidneys and serosal membranes.

Autoimmune hepatitis, also called chronic active hepatitis, also can be treated with a 6-MP drug and the dose optimized using the methods of the invention. Autoimmune hepatitis is a chronic inflammation of the liver occurring as a sequel to hepatitis B or non-A, non-B hepatitis and is characterized by infiltration of portal areas by plasma cells and macrophages, piecemeal necrosis, and fibrosis.

The methods of the invention also can be useful for treating pemphigus vulgaris, the most common and severe form of pemphigus, which is a chronic, relapsing and sometimes fatal skin disease characterized clinically by the development of successive crops of vesicles and bullae and treated by azathioprine. This disorder is characterized histologically by acantholysis, and immunologically by serum autoantibodies against antigens in the intracellular zones of the epidermis.

The methods of the invention can also be used to optimize the therapeutic efficacy of 6-MP drug treatment of graft versus host disease, which can occur in transplant patients. Graft versus host disease occurs when a transplant patient has an immune reaction to the non-self transplant organ or tissue. The methods of the invention for optimizing the therapeutic efficacy of 6-MP drug treatment is particularly useful for treating heart, kidney and liver transplant recipients. The methods of the invention can be used to optimize therapeutic efficacy and/or minimize toxicity associated with 6-MP drug treatment of a transplant patient.

The following examples are intended to illustrate but not limit the present invention.

EXAMPLE I

6-Mercaptopurine Metabolite Levels Predict Clinical Efficacy and Drug Toxicity in Pediatric IBD

This example describes measuring 6-MP metabolite levels and correlation with the response of IBD patients treated with a 6-MP drug.

The levels of the 6-MP metabolites 6-TG and 6-MMP were measured in IBD patients to whom 6-MP pro-drug was administered, and the relationship of 6-MP metabolites to clinical disease activity and drug toxicity was determined. Briefly, blood was sampled (n=89) prior to daily administration of 6-MP in 55 IBD patients (CD n=51, UC n=4) receiving 1–1.5 mg/kg/day over at least a 4 month period (≧4 mo.). When AZA was administered, a conversion factor of 2.07 was used to convert to the equivalent 6-MP dose. Twice as much AZA is administered relative to 6-MP to have an equivalent dose of 6-MP.

Erythrocyte 6-TG, 6-MMP and 6-MP thiobases were measured (pmol/8×10^8 RBC) using reverse phase HPLC. Briefly, blood samples were collected in EDTA (ethylene diamine tetraacetic acid) as anticoagulant. Cells were centrifuged and washed three times with an equal volume of 0.9% saline. Washed packed cells were stored at −70° C. until analysis was performed.

For acid hydrolysis, 500 μl deionized H_2O, 50 μl thawed red blood cells, 40 μl of the appropriate standard or control, 500 μl 3.0 N H_2SO_4, and 300 μl 10 mM dithiothreitol (DTT) was added to an 8 ml glass screw cap tube. The capped tubes were placed in a heating block preheated to 100° C. and hydrolyzed. For 6-MMP, hydrolysis was carried out for 5 hours. For 6-MP and 6-TG, hydrolysis was carried out for 1 hour. After the incubation, tubes were cooled in a room temperature water bath. To tubes hydrolyzed for 5 hours (6-MMP), 400 μl 3.4 N NaOH and 1.0 ml 2 M Tris buffer, pH 9.0 was added. To tubes hydrolyzed for 1 hour (6-MP/6-TG), 450 μl 3.4 N NaOH and 500 μl 2M Tris base was added. A volume of 4 ml 0.03% phenylmercuric chloride in methylene chloride was added to each tube. The tubes were capped and lightly agitated on a bi-directional rotator (15 min for 6-MMP and 30 min for 6-MP/6-TG). The contents were transferred to a 15 ml polypropylene centrifuge tube and centrifuged at 3500 rpm for 3 min at 10° C. The aqueous phase (top layer) was discarded, and 3.0 ml of the organic phase (bottom layer) was transferred to a clean 15 ml polypropylene centrifuge tube. The analytes in the organic phase were back extracted by adding 225 μl 0.1 N HCl and lightly mixing on an orbital rotator for 5 min. Following vortexing for 30 seconds, the tubes were centrifuged at 3500 rpm for 3 min at 10° C.

For 6-MMP analysis, 50 μl analyte was analyzed on a C18 reverse phase column with the mobile phase containing 1 mM DTT, 2.078% triethylamine and 4% methanol, adjusted to pH 3.2 with concentrated H_3PO_4. For 6-MP and 6-TG analysis, 100 μl analyte was analyzed on a C18 reverse phase column using 0.1 M H_3PO_4 and 1 mM DTT in H_2O as the mobile phase.

Hepatic, pancreatic and hematological tests were obtained every 3 months. Clinical remission was defined as a Harvey Bradshaw Index<5 in those patients off corticosteroids or weaned to a level of prednisone≦0.4 mg/kg/od (administered every other day). Treatment failures were defined as non-responders (HBI>5 or steroid dependence) or cessation of 6-MP due to side effects.

As shown in Table 1, a 6-TG level of >225 pmol per 8×10^8 RBC was associated with remission. The median

values shown in the tables represent pmol of the indicated 6-MP metabolite per $8x10^8$ RBC. Excessive 6-TG and 6-MMP levels were associated with leukopenia and hepatotoxicity, respectively. Negligible metabolite levels detected non-compliance as a cause of treatment failure in 2/31 cases. These results indicate that 6-MP metabolite levels predict both clinical responsiveness and drug-related toxicity.

TABLE 1

Group	n	median 6-TG	6-TG >225	median 6-MMP
Responders	58	295	45/58 (78%)	3094
Non-responders	31	194*	8/31 (26%)	2048
Hepatic toxicity	7	258	5/7	9211**
Pancreatic toxicity	6	231	2/6	2342
Hematologic toxicity	6	414◇	5/5	7042
p Values		*<0.001 ◇<0.03	‡<0.001	**<0.001

These results demonstrate that determining levels of 6-MP metabolites is useful for predicting efficacy and toxicity of 6-MP drug therapy administered to IBD patients.

EXAMPLE II

6-Mercaptopurine Metabolite Levels Correlate with Optimal 6-MP Therapy in IBD Patients

This example describes prospective examination of the correlation of 6-MP metabolite levels with therapeutic response to 6-MP drug therapy and 6-MP drug related toxicity in IBD patients treated with 6-MP.

To obtain additional statistical data on IBD patients treated with a 6-MP drug, additional patients and samples were analyzed and combined with the data obtained in Example I. Blood was sampled at least once in 93 IBD patients followed at Sainte-Justine Hospital IBD Center, Montreal, Canada, who were administered 6-MP drug therapy for at least 4 months. The 93 patients were pediatric patients, with 80 diagnosed as having CD, 8 diagnosed as having UC, and 5 diagnosed as having indeterminate colitis (CD or UC). All but 7 patients were given AZA. The dosages were converted to 6-MP equivalents using a factor of 2.07 as described in Example I. For some patients, two or more samples were obtained and analyzed. Response to 6-MP was defined by clinical remission (HBI<5, closed fistula) without corticosteroids. Disease activity and physical exam were ascertained at each clinic visit at which 6-MP metabolite levels were determined (clinical evaluation point). Hematological, pancreatic and hepatic laboratory parameters were evaluated simultaneously. Erythrocyte 6-TG and 6-MMP concentrations (pmol/$8x10^8$ RBC) were measured by HPLC (Cuffari et al., supra, 1996a).

The results of the analysis of 6-MP metabolites in IBD patients are shown in Table 2. The number of samples corresponds to the number of different samples obtained from the 93 patients. 6-TG quartile analysis, in which values are determined at 25, 50 and 75% of the data set, revealed that the frequency of response significantly increased at levels>230 pmol/$8x10^8$ RBC ($p<0.01$). Among patients in relapse, only 28% of patients had 6-TG levels>230 pmol/$8x10^8$ RBC. In contrast, 65% of patients in remission had 6-TG levels>230 pmol/$8x10^8$ RBC ($p<0.01$). Therefore, erythrocyte 6-TG concentrations were significantly and independently associated with therapeutic response to 6-MP drug therapy.

The induction and maintenance of remission was found to be optimal at 6-TG levels>230 pmol/$8x10^8$ RBC. 78% of patients above a median 6-TG of 230 pmol/$8x10^8$ RBC were responders (see FIG. 3). These results indicate that a 6-TG value of 230 pmol/$8x10^8$ RBC can be used to predict efficacy of drug treatment with a 6-MP drug such as 6-MP or azathioprine.

TABLE 2

Clinical evaluation point	(n)	Median 6-TG	Median 6-MMP	Median dose (mg/kg/day)
Remission	106	309*	2600	1.3
Relapse	72	197	1602	1.25
*p value		<0.0001	0.3	0.4

Toxicity in the IBD patients treated with a 6-MP drug was also evaluated. Toxicity was measured essentially as described previously (Cuffari et al., supra, 1996a) . Thirty six patients (39%) experienced an adverse event. Hepatotoxicity was observed in 17% of patients, measured as the serum level of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (ALT, AST; exceeding or greater than 2xupper limit of normal) . Leukopenia was observed in 14% of patients (white blood cell (WBC)<4000). Pancreatic toxicity was observed in 7% of patients (lipase/amylase>2x N) . High 6-MMP levels correlated significantly with hepatotoxicity (5463 with hepatotoxicity versus 2177 without hepatotoxicity; $p=0.04$). Leukopenia was observed in only 8% (8/106) of samples from patients in remission, with significantly higher 6-TG levels observed in these patients (mean value of 490 in patients with leukopenia versus mean value of 323 without leukopenia; $p<0.04$; median values were 342 versus 307, respectively). Therefore, leukopenia did not correlate with therapeutic efficacy. Furthermore, drug dose (per kg) did not correlate with therapeutic efficacy (see Table 2). However, those patients who do develop leukopenia have a higher 6-TG level than the rest of the responder group. These results indicate that 6-TG levels should be monitored to avoid potential clinical bone marrow suppression in responder patients who have high levels of 6-TG.

These results demonstrate a significant correlation between erythrocyte 6-TG levels and the therapeutic response to 6-MP drug treatment in IBD patients. The induction and maintenance of remission was found to be optimal at 6-TG levels>230 pmol/$8x10^8$ RBC. Therefore, monitoring 6-MP metabolite levels, in particular 6-TG, is useful for determining that a therapeutically effective concentration of 6-MP metabolites is maintained while treating IBD patients with a 6-MP drug. Monitoring 6-MP metabolite levels, in particular 6-TG and 6-MMP, is also useful for minimizing 6-MP drug related toxicity.

EXAMPLE III

Gender and Age Differences in Metabolism of a 6-MP Drug

This example describes gender and age differences observed in pediatric patients treated with 6-MP drug therapy.

Pediatric IBD patients undergoing 6-MP drug therapy were assessed for levels of 6-MP metabolites. These patients were wild type for TPMT. Patients were assessed based on gender and age as it relates to puberty. Puberty is established at 12 years of age in girls and 14 years of age in boys.

As shown in Table 3, the 6-MMP values are much lower in boys after puberty (greater than 14 years). Since the total amount of thiometabolites is lower, this indicates that either lower doses of 6-MP are used or that there is a difference in the bioavailability of 6-MP after puberty in males.

TABLE 3

6-MP Metabolite Levels in Pediatric IBD Patients

	Number Observed	6-TG level (pmol per 8×10^8 RBC)	6-MMP level (pmol per 8×10^8 RBC)	Ratio 6-MMP/6-TG
Girls (0–12 y)	39	182.2	3447.0	18.52
Girls (>12 y)	116	217.2	3304.5	12.55
Boys (0–14 y)	51	235.0	3681.6	17.24
Boys (>14 y)	104	222.5	1662.3*	6.78*

*$p < 0.001$

These results demonstrate that gender and age can affect the metabolism of 6-MP in pediatric IBD patients undergoing 6-MP drug therapy.

EXAMPLE IV

Thiopurine Methyltransferase (TPMT) Genotyping and Responsiveness to 6-MP Drug Therapy

This example describes TPMT genotyping of IBD patients treated with 6-MP drug therapy.

The genotype of TPMT was determined in IBD patients that were responders and non responders. Genotyping of TPMT was measured essentially as described previously (Baccichet et al., *Leuk. Res.* 21:817–823 (1997); Ziekiewicz et al., *Gene* 205:161–171 (1997)). The data shown in Table 4 indicate that patients heterozygous for the TPMT mutation had significantly higher 6-TG levels compared to those patients without the mutation. All heterozygote patients were responders to 6-MP.

TABLE 4

TPMT Genotyping of IBD Patients

	Heterozygote	Normal
Responder	100%	55%
Non responder	0%	45%
mean 6-TG	589*	247

p value *less than 0.0001

TPMT genotyping revealed that 8 of 93 (9%) of patients were heterozygotes. No homozygous TPMT deficient patients were detected. All 8 heterozygotes responded to 6-MP and had 6-TG levels>230 pmol/8×10^8 RBC.

These results demonstrate that TPMT genotyping is useful for predicting the effectiveness of 6-MP therapy in an IBD patient. Heterozygote patients are expected to have lower TPMT activity and should therefore be monitored for high levels of 6-TG for possible toxic levels associated with leukopenia or bone marrow suppression. 6-MP drug doses can be reduced accordingly. Wild type homozygous patients are expected to have higher TPMT activity and should therefore be monitored to maintain an effective therapeutic level of 6-TG and to determine if patients develop toxic levels of 6-MMP. Homozygous patients deficient in TPMT activity can be treated with lower doses of a 6-MP drug provided that patients are closely monitored for toxicity such as leukopenia.

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the claims.

We claim:

1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

2. The method of claim 1, wherein said immune-mediated gastrointestinal disorder is inflammatory bowel disease (IBD).

3. The method of claim 2, wherein said subject having IBD is a pediatric subject.

4. The method of claim 1, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

5. The method of claim 1, wherein said level of 6-thioguanine is determined in red blood cells.

6. The method of claim 5, wherein said level is determined using high pressure liquid chromatography.

7. A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and

(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

8. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is IBD.

9. The method of claim 8, wherein said subject having IBD is a pediatric subject.

10. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

11. The method of claim 7, wherein said toxicity associated with said drug treatment is hematologic toxicity.

12. The method of claim 7, wherein said toxicity associated with said drug treatment is hepatic toxicity.

13. The method of claim 7, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

14. The method of claim 13, wherein said level is determined using high pressure liquid chromatography.

15. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and

(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject,

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject, and

wherein the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

16. The method of claim 15, wherein said immune-mediated gastrointestinal disorder is IBD.

17. The method of claim 16, wherein said subject having IBD is a pediatric subject.

18. The method of claim 15, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

19. The method of claim 15, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

20. The method of claim 19, wherein said level is determined using high pressure liquid chromatography.

21. The method of claim 15, wherein said toxicity associated with said drug treatment is selected from the group consisting of hepatic toxicity and hematologic toxicity.

22. A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said non-IBD autoimmune disease; and

(b) determining the level of 6-thioguanine in said subject having said non-IBD autoimmune disease,

wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to said subject.

23. The method of claim 22, wherein said level of 6-thioguanine metabolite is determined in red blood cells.

24. The method of claim 23, wherein said level is determined using high pressure liquid chromatography.

25. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and

(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject, and

wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

26. The method of claim 25, wherein said immune-mediated gastrointestinal disorder is IBD.

27. The method of claim 26, wherein said subject having IBD is a pediatric subject.

28. The method of claim 25, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

29. The method of claim 25, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

30. The method of claim 29, wherein said level is determined using high pressure liquid chromatography.

31. The method of claim 25, wherein said toxicity associated with said drug treatment is selected from the group consisting of hepatic toxicity and hematologic toxicity.

32. The method of claim 1, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

33. The method of claim 7, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

34. The method of claim 15, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

35. The method of claim 22, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

36. The method of claim 25, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.

37. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptoriboside to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine or 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder;

wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject, and

wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

38. The method of claim 37, wherein said drug is 6-mercaptopurine.

39. The method of claim 37, wherein said drug is azathioprine.

40. The method of claim 37, wherein said immune-mediated gastrointestinal disorder is inflammatory bowel disease (IBD).

41. The method of claim 40, wherein said subject having IBD is a pediatric subject.

42. The method of claim 37, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

43. The method of claim 37, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

44. The method of claim 43, wherein said level is determined using high pressure liquid chromatography.

45. The method of claim 37, wherein said toxicity associated with said drug treatment is selected from the group consisting of hepatic toxicity and hematologic toxicity.

46. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) determining the level of 6-thioguanine or 6-methyl-mercaptopurine in a subject administered a drug selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptoriboside, said subject having said immune-mediated gastrointestinal disorder;

wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the, amount of said drug subsequently administered to said subject, and

wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

47. The method of claim 46, wherein said drug is 6-mercaptopurine.

48. The method of claim 46, wherein said drug is azathioprine.

49. The method of claim 46, wherein said immune-mediated gastrointestinal disorder is IBD.

50. The method of claim 47, wherein said subject having IBD is a pediatric subject.

51. The method of claim 46, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

52. The method of claim 46, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

53. The method of claim 52, wherein said level is determined using high pressure liquid chromatography.

54. The method of claim 46, wherein said toxicity associated with said drug treatment is selected from the group consisting of hepatic toxicity and hematologic toxicity.

* * * * *

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(12) **United States Patent**
Seidman et al.

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(54) **METHODS OF OPTIMIZING DRUG THERAPEUTIC EFFICACY FOR TREATMENT OF IMMUNE-MEDIATED GASTROINTESTINAL DISORDERS**

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(57) **ABSTRACT**

The present invention provides a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder such as inflammatory bowel disease. The method of the invention includes the step of determining the level of one or more 6-mercaptopurine metabolites in the patient having an immune-mediated gastrointestinal disorder.

32 Claims, 3 Drawing Sheets

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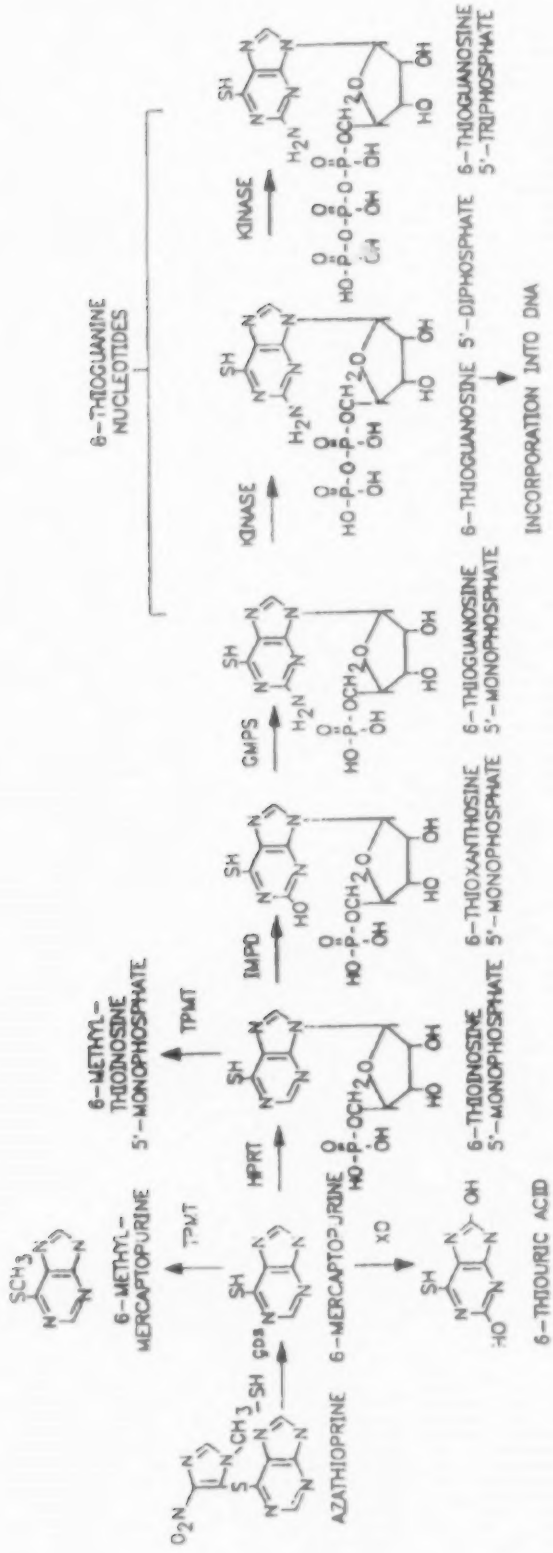
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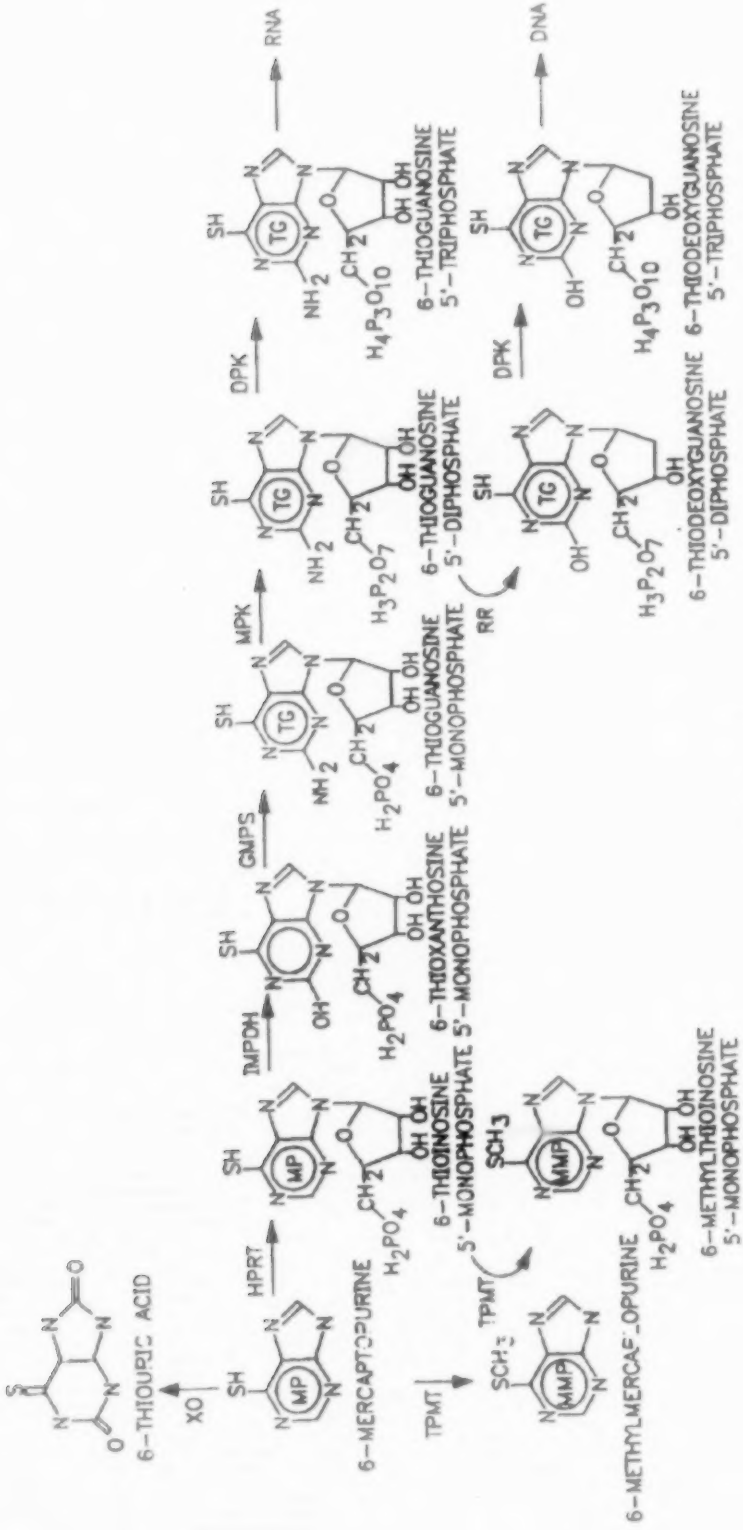
6-METHYL-MERCAPTOPURINE
6-METHYL-THIOINOSINE 5'-MONOPHOSPHATE
6-THIOINOSINE 5'-MONOPHOSPHATE
6-THIOXANTHOSINE 5'-MONOPHOSPHATE
6-THIOGUANOSINE 5'-MONOPHOSPHATE
6-THIOGUANOSINE 5'-DIPHOSPHATE
6-THIOGUANOSINE 5'-TRIPHOSPHATE
6-THIOURIC ACID
6-THIOGUANINE NUCLEOTIDES
INCORPORATION INTO DNA
GDS
HPRT
TPMT
IMPD
GMPS
KINASE
KINASE
XO

FIG. 1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RR
DPK
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RNA
DNA

FIG. 2

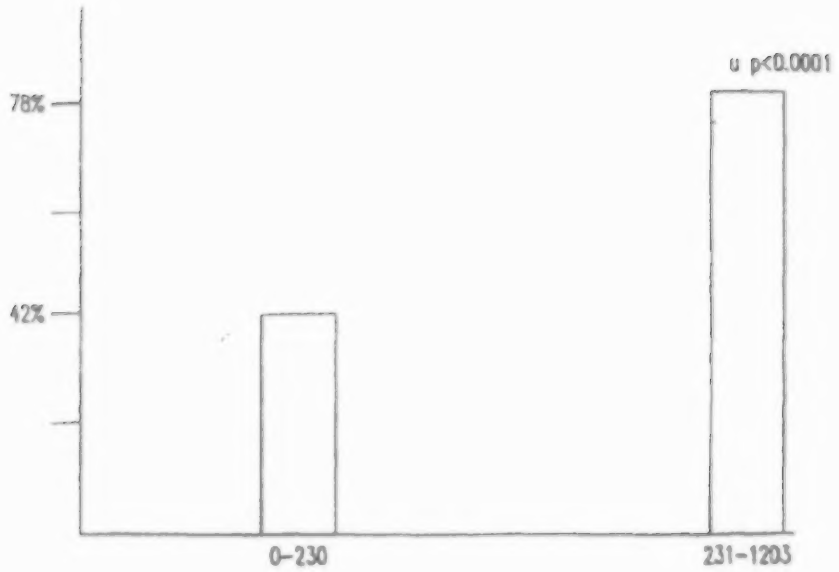

FIG. 3

METHODS OF OPTIMIZING DRUG THERAPEUTIC EFFICACY FOR TREATMENT OF IMMUNE-MEDIATED GASTROINTESTINAL DISORDERS

This application is a continuation of application Ser. No. 09/288,344, filed Apr. 8, 1999, now U.S. Pat. No. 6,355,623, issued Mar. 12, 2002, which is incorporated herein by reference and which claims benefit of provisional application Ser. No. 60/101,714, filed Sep. 24, 1998, now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates generally to autoimmunity and immune-mediated gastrointestinal disorders such as inflammatory bowel disease and more specifically to methods for optimizing treatment of immune-mediated gastrointestinal disorders.

BACKGROUND INFORMATION

Immune-mediated gastrointestinal disorders encompass a wide range of debilitating gastrointestinal diseases of various etiologies. One such immune-mediated gastrointestinal disorder, inflammatory bowel disease (IBD), is the collective term used to describe two gastrointestinal disorders of unknown etiology: Crohn's disease (CD) and ulcerative colitis (UC). The course and prognosis of IBD, which occurs world-wide and is reported to afflict as many as two million people, varies widely. Onset of IBD is predominantly in young adulthood with diarrhea, abdominal pain, and fever the three most common presenting symptoms. The diarrhea may range from mild to severe and in ulcerative colitis often is accompanied by bleeding. Anemia and weight loss are additional common signs of IBD. Ten percent to fifteen percent of all patients with IBD will require surgery over a ten year period. In addition, patients with IBD are at increased risk for the development of intestinal cancer. Reports of an increasing occurrence of psychological problems, including anxiety and depression, are perhaps not surprising symptoms of what is often a debilitating disease that strikes people in the prime of life.

6-Mercaptopurine (6-MP) and azathioprine (AZA), a prodrug that is non-enzymatically converted to 6-mercaptopurine (6-MP), are 6-MP drugs that can be used as an effective treatment for inflammatory bowel diseases such as Crohn's disease and ulcerative colitis (Kirschner *Gastroenterology* 115:813–821 (1998)). 6-MP can be enzymatically converted to various 6-MP metabolites, including 6-methyl-mercaptopurine (6-MMP) and 6-thioguanine (6-TG) and their nucleotides. 6-TG nucleotides are thought to be the active metabolite in mediating many of the effects of 6-MP drug treatment.

Thiopurine methyltransferase (TPMT) is a cytoplasmic enzyme that preferentially catalyzes the S-methylation of 6-MP and 6-TG to form S-methylated metabolites such as 6-MMP and 6-methylthioguanine (6-MTG), respectively. TPMT exhibits genetic polymorphism, with 89% of Caucasians and African Americans having high activity, 11% intermediate activity and 1 in 300 TPMT deficient. Clinical studies with AZA and 6-MP have shown an inverse relationship between TPMT activity and 6-TGN accumulation. Patients who less efficiently methylate these thiopurines have more extensive conversion to 6-TGN, which can lead to potentially fatal hematopoietic toxicity. Therefore, patients who have less active TPMT can be more susceptible to toxic side effects of 6-MP therapy.

Although drugs such as 6-MP and AZA have been used for treating IBD, non-responsiveness and drug toxicity unfortunately complicate treatment in some patients. Complications associated with 6-MP drug treatment include allergic reactions, neoplasia, opportunistic infections, hepatitis, bone marrow suppression, and pancreatitis. Therefore, many physicians are reluctant to treat patients with AZA because of its potential side effects, especially infection and neoplasia.

Thus, there exists a need to develop methods to optimize the dose of 6-mercaptopurine drugs and assess biotransformation in individual patients to optimize the therapeutic efficacy of 6-mercaptopurine drugs while minimizing toxic side effects. The present invention satisfies this need and provides related advantages as well.

SUMMARY OF THE INVENTION

The present invention provides a method of optimizing therapeutic efficacy of 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder. The method includes the steps of administering a 6-mercaptopurine drug to a subject having an immune-mediated gastrointestinal disorder; and determining a level of 6-thioguanine in the subject having the immune-mediated gastrointestinal disorder, where a level of 6-thioguanine less than a level corresponding to about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to the subject and where a level of 6-thioguanine greater than a level corresponding to about 400 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject. The methods are directed to treating immune-mediated gastrointestinal disorders, including inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease. In a method of optimizing therapeutic efficacy of 6-mercaptopurine treatment of IBD, the subject having IBD can be, for example, a pediatric subject. The level of 6-thioguanine can be determined, for example, in red blood cells using high pressure liquid chromatography.

The present invention also provides a method of reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder. The method of reducing toxicity associated with an immune-mediated gastrointestinal disorder includes the steps of administering a 6-mercaptopurine drug to a subject having the immune-mediated gastrointestinal disorder; and determining a level of a 6-mercaptopurine metabolite in the subject having the immune-mediated gastrointestinal disorder, where a level of the 6-mercaptopurine metabolite greater than a predetermined toxic level of the 6-mercaptopurine metabolite indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby reducing toxicity associated with 6-mercaptopurine drug treatment of the immune-mediated gastrointestinal disorder. In a method of the invention, the 6-mercaptopurine metabolite can be, for example, 6-thioguanine and the predetermined toxic level of 6-thioguanine can correspond, for example, to a level of about 400 pmol per 8×10^8 red blood cells. Where the elevated 6-mercaptopurine metabolite is 6-thioguanine, the toxicity associated with 6-mercaptopurine treatment can be, for example, hematologic toxicity. The 6-mercaptopurine metabolite also can be a metabolite such as 6-methyl-mercaptopurine and the pre-

determined toxic level of 6-methyl-mercaptopurine can correspond, for example, to a level of about 7000 pmol per $8x10^8$ red blood cells. Where the elevated 6-mercaptopurine metabolite is 6-methyl-mercaptopurine, the toxicity associated with 6-mercaptopurine treatment can be, for example, hepatic toxicity.

Further provided by the invention is a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder. The method includes the steps of administering a 6-mercaptopurine drug to a subject having an immune-mediated gastrointestinal disorder; determining a level of 6-thioguanine in the subject having the immune-mediated gastrointestinal disorder; and determining a level of 6-methyl-mercaptopurine in the subject having the immune-mediated gastrointestinal disorder, where a level of 6-thioguanine less than a predetermined minimal therapeutic level indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby increasing therapeutic efficacy; where a level of 6-thioguanine greater than a predetermined toxic level of 6-thioguanine indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby reducing toxicity associated with 6-mercaptopurine treatment of the immune-mediated gastrointestinal disorder; and where a level of 6-methyl-mercaptopurine greater than a predetermined toxic level of 6-methyl-mercaptopurine indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to the subject, thereby reducing toxicity associated with 6-mercaptopurine treatment of the immune-mediated gastrointestinal disorder.

In such a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder, the predetermined minimal therapeutic level of 6-thioguanine can be, for example, a level corresponding to about 230 pmol per $8x10^8$ red blood cells; the predetermined toxic level of 6-thioguanine can be, for example, a level corresponding to about 400 pmol per $8x10^8$ red blood cells; and the predetermined toxic level of 6-methyl-mercaptopurine can be, for example, a level corresponding to about 7000 pmol per $8x10^8$ red blood cells. The level of 6-thioguanine and 6-methyl-mercaptopurine each can be conveniently determined, for example, in red blood cells using high pressure liquid chromatography. The invention further provides methods to optimize the therapeutic efficacy of 6-mercaptopurine drug treatment of a non-IBD autoimmune disease.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows mercaptopurine metabolism and the structures of 6-mercaptopurine (6-MP) metabolites. The initial metabolism of 6-MP is catalyzed by thiopurine methyltransferase (TPMT), xanthine oxidase (XO), and hypoxanthine phosphoribosyltransferase (HPRT). Further metabolism of the thionucleotide is catalyzed by inosine monophosphate dehydrogenase (IMPD) and guanosine monophosphate synthetase (GMPS). The breakdown of azathioprine to 6-mercaptopurine is nonenzymatic.

FIG. 2 shows 6-mercaptopurine (6-MP) metabolism and the 6-MP metabolites that are measured as 6-MP, 6-thioguanine (6-TG) and 6-methyl-mercaptopurine (6-MMP) (indicated as "MP," "TG" and "MMP" inside the base). 6-TG mono-phosphate is converted to the di- and tri-phosphate by monophosphate kinase (MPK) and diphosphate kinase (DPK), respectively. The ribonucleoside diphosphate is converted to deoxyribonucleoside diphosphate by ribonucleotide reductase (RR).

FIG. 3 shows ranges of 6-thioguanine in IBD patients treated with a 6-MP drug.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of optimizing therapeutic efficacy of 6-mercaptopurine (6-MP) drug treatment of an immune-mediated gastrointestinal disorder. The method includes the steps of administering a 6-MP drug to a subject having an immune-mediated gastrointestinal disorder; and determining a level of 6-thioguanine (6-TG) in the subject having the immune-mediated gastrointestinal disorder, where a level of 6-TG less than a level corresponding to about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of 6-MP drug subsequently administered to the subject and where a level of 6-TG greater than a level corresponding to about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject. The methods are directed to treating immune-mediated gastrointestinal disorders, including inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease. In a method of optimizing therapeutic efficacy of 6-MP treatment of IBD, the subject having IBD can be, for example, a pediatric subject. The level of 6-TG can be determined, for example, in red blood cells using high pressure liquid chromatography (HPLC).

The invention provides methods of optimizing therapeutic efficacy of 6-MP drug treatment of an immune-mediated gastrointestinal disorder. The methods of the invention are particularly useful for treating an immune-mediated gastrointestinal disorder such as IBD, including Crohn's disease and ulcerative colitis and subtypes thereof. The methods of the invention allow the clinician to provide an individually optimized dosage of a 6-MP drug so as to achieve a target level of a 6-MP metabolite in a particular patient having an immune-mediated gastrointestinal disorder, thereby optimizing the effectiveness of 6-MP drug therapy in the patient. The methods of the invention for optimizing therapeutic efficacy of 6-MP drug treatment involve determining the level of 6-TG in a patient having an immune-mediated gastrointestinal disorder. As disclosed herein, the level of 6-TG measured in a patient treated with a 6-MP drug was an indicator of the effectiveness of drug treatment. A level of at least 230 pmol 6-TG/$8x10^8$ red blood cells (RBC) was found in responders to drug therapy (see Examples I and II). These results indicate that determining the level of 6-TG can be used to assess whether a patient has a level of 6-TG that is sufficient to alleviate symptoms of an immune-mediated gastrointestinal disorder such as IBD, thus optimizing therapeutic efficacy.

As used herein, the term "6-mercaptopurine drug" or "6-MP drug" refers to any drug that can be metabolized to an active 6-mercaptopurine metabolite that has therapeutic efficacy such as 6-TG. Exemplary 6-mercaptopurine drugs as defined herein include 6-mercaptopurine (6-MP) and azathioprine (AZA). As illustrated in FIG. 1, both of 6-MP and AZA can be metabolized to 6-mercaptopurine metabolites such as the exemplary 6-mercaptopurine metabolites shown in FIG. 1, including 6-thioguanine (6-TG), 6-methyl-

mercaptopurine (6-MMP) and 6-thiouric acid. (Lennard, *Eur. J. Clin. Pharmacol.* 43:329–339 (1992)).

Other 6-MP drugs include, for example, 6-methylmercaptopurine riboside and 6-TG (Loo et al., *Clin. Pharmacol. Ther.* 9:180–194 (1968); O'Dwyer et al., *J. Natl. Cancer Inst.* 83:1235–1240 (1991); Erb et al., *Cancer Chemother. Pharmacol.* 42:266–272 (1998); Lancaster et al., *Br. J. Haematol.* 102:439–443 (1998); Ingle et al., *Am. J. Clin. Oncol.* 20:69–72 (1997); Evans and Relling, *Leuk. Res.* 18:811–814 (1994)). 6-TG is a particularly useful 6-MP drug in patients having high TPMT activity. Patients exhibiting high TPMT activity are expected to more easily convert 6-MP drugs such as 6-MP and AZA to 6-MMP (see FIGS. 1 and 2). As disclosed herein, high levels of 6-MMP are associated with hepatotoxicity (see Examples I and II). Therefore, patients with high TPMT activity can be more susceptible to toxic effects of 6-MP drug therapy. By administering 6-TG, which is an active 6-MP metabolite associated with therapeutic efficacy (see Examples I and II), the toxicity that can be associated with conversion of 6-MP to 6-MMP is bypassed.

It is understood that the 6-MP metabolites can be the metabolites shown in FIG. 1 or analogues thereof. As used herein, the term "6-thioguanine" or "6-TG" refers to 6-thioguanine or analogues thereof, including molecules having the same base structure, for example, 6-thioguanine ribonucleoside, 6-thioguanine ribonucleotide mono-, di- and tri-phosphate, 6-thioguanine deoxyribonucleoside and 6-thioguanine deoxyribonucleotide mono-, di, and triphosphate. The term "6-TG" also includes derivatives of 6-thioguanine, including chemical modifications of 6-TG, so long as the structure of the 6-TG base is preserved.

As used herein, the term "6-methyl-mercaptopurine" or "6-MMP" refers to 6-methyl-mercaptopurine or analogues thereof, including analogues having the same base structure, for example, 6-methyl-mercaptopurine ribonucleoside, 6-methyl-mercaptopurine ribonucleotide mono-, di-, and tri-phosphate, 6-methyl-mercaptopurine deoxyribonucleoside, and 6-methyl-mercaptopurine deoxyribonucleotide mono-, di- and tri-phosphate. The term "6-MMP" also includes derivatives of 6-methyl-mercaptopurine, including chemical modifications of 6-MMP, so long as the structure of the 6-MMP base is preserved.

The methods of the invention relate to treatment of an immune-mediated gastrointestinal disorder. As used herein, the term "immune-mediated gastrointestinal disorder" or "immune-mediated GI disorder" refers to a non-infectious disease of the gastrointestinal tract or bowel that is mediated by the immune system or cells of the immune system. Immune-mediated gastrointestinal disorders include, for example, inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis, lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

The methods of the invention are particularly useful for treating IBD, or subtypes thereof, which has been classified into the broad categories of Crohn's disease and ulcerative colitis. As used herein, "a subject having inflammatory bowel disease" is synonymous with the term "a subject diagnosed with having an inflammatory bowel disease," and means a patient having Crohn's disease or ulcerative colitis. Crohn's disease (regional enteritis) is a disease of chronic inflammation that can involve any part of the gastrointestinal tract. Commonly, the distal portion of the small intestine (ileum) and cecum are affected. In other cases, the disease is confined to the small intestine, colon or anorectal region. Crohn's disease occasionally involves the duodenum and stomach, and more rarely the esophagus and oral cavity.

The variable clinical manifestations of Crohn's disease are, in part, a result of the varying anatomic localization of the disease. The most frequent symptoms of CD are abdominal pain, diarrhea and recurrent fever. CD is commonly associated with intestinal obstruction or fistula, which is an abnormal passage between diseased loops of bowel, for example. Crohn's disease also includes complications such as inflammation of the eye, joints and skin; liver disease; kidney stones or amyloidosis. In addition, CD is associated with an increased risk of intestinal cancer.

Several features are characteristic of the pathology of Crohn's disease. The inflammation associated with CD, known as transmural inflammation, involves all layers of the bowel wall. Thickening and edema, for example, typically also appear throughout the bowel wall, with fibrosis also present in long-standing disease. The inflammation characteristic of CD also is discontinuous in that segments of inflamed tissue, known as "skip lesions," are separated by apparently normal intestine. Furthermore, linear ulcerations, edema, and inflammation of the intervening tissue lead to a "cobblestone" appearance of the intestinal mucosa, which is distinctive of CD.

A hallmark of Crohn's disease is the presence of discrete aggregations of inflammatory cells, known as granulomas, which are generally found in the submucosa. Some Crohn's disease cases display the typical discrete granulomas, while others show nonspecific transmural inflammation. As a result, the presence of discrete granulomas is indicative of CD, although the absence of granulomas also is consistent with the disease. Thus, transmural or discontinuous inflammation, rather than the presence of granulomas, is a preferred diagnostic indicator of Crohn's disease (Rubin and Farber, *Pathology* (Second Edition) Philadelphia: J. B. Lippincott Company (1994)).

Ulcerative colitis (UC) is a disease of the large intestine characterized by chronic diarrhea with cramping abdominal pain, rectal bleeding, and loose discharges of blood, pus and mucus. The manifestations of ulcerative colitis vary widely. A pattern of exacerbations and remissions typifies the clinical course of most UC patients (70%), although continuous symptoms without remission are present in some patients with UC. Local and systemic complications of UC include arthritis, eye inflammation such as uveitis, skin ulcers and liver disease. In addition, ulcerative colitis and especially long-standing, extensive disease is associated with an increased risk of colon carcinoma.

Several pathologic features characterize UC in distinction to other inflammatory bowel diseases. Ulcerative colitis is a diffuse disease that usually extends from the most distal part of the rectum for a variable distance proximally. The term left-sided colitis describes an inflammation that involves the distal portion of the colon, extending as far as the splenic flexure. Sparing of the rectum or involvement of the right side (proximal portion) of the colon alone is unusual in ulcerative colitis. The inflammatory process of ulcerative colitis is limited to the colon and does not involve, for example, the small intestine, stomach or esophagus. In addition, ulcerative colitis is distinguished by a superficial inflammation of the mucosa that generally spares the deeper layers of the bowel wall. Crypt abscesses, in which degenerated intestinal crypts are filled with neutrophils, also are typical of ulcerative colitis (Rubin and Farber, supra, 1994).

In comparison with Crohn's disease, which is a patchy disease with frequent sparing of the rectum, ulcerative colitis is characterized by a continuous inflammation of the colon that usually is more severe distally than proximally. The inflammation in ulcerative colitis is superficial in that it is usually limited to the mucosal layer and is characterized by an acute inflammatory infiltrate with neutrophils and crypt abscesses. In contrast, Crohn's disease affects the entire thickness of the bowel wall with granulomas often, although not always, present. Disease that terminates at the ileocecal valve, or in the colon distal to it, is indicative of ulcerative colitis, while involvement of the terminal ileum, a cobblestone-like appearance, discrete ulcers or fistulas suggest Crohn's disease.

In addition to IBD, immune-mediated GI disorders also include other gastrointestinal diseases such as lymphocytic colitis; microscopic colitis; collagenous colitis; autoimmune enteropathy, including autoimmune enteritis and autoimmune enterocolitis; allergic gastrointestinal disease; and eosinophilic gastrointestinal disease, including eosinophilic gastroenteritis and eosinophilic enteropathy.

Over the past two decades, the histological evaluation of colorectal biopsies obtained by colonoscopy has expanded the spectrum of chronic IBD. A new group of immune-mediated bowel disorders has emerged, characterized by chronic watery diarrhea, minimal or absent endoscopic findings, and inflammatory changes in mucosal biopsies. Lymphocytic colitis, also commonly referred to as microscopic colitis, is a clinicopathological syndrome characterized primarily by lymphocytic infiltration of the epithelium. Collagenous colitis is defined by the presence of a collagenous band below the surface epithelium, accompanied by an increase in inflammatory cell infiltrate (Lazenby et al. *Hum. Pathol.* 20:18–28 (1989)). These disorders are often associated with other autoimmune diseases such as rheumatoid arthritis, pernicious anemia, thyroiditis, uveitis and type I diabetes mellitus. Clinicians have used immunosuppressive drugs, including 6-MP, to treat these disorders (Dealandres et al. *J. Pediatr. Gastroenterol. Nutr.* 25:341–346 (1997)).

Autoimmune enteropathy, including autoimmune enteritis and autoimmune enterocolitis, is a syndrome of severe secretory diarrhea and marked enterocolitis, in association with diagnostic circulating antibodies to enterocytes (Seidman et al., *J. Pediatr.* 117:929–932 (1990)). This syndrome, most often seen in infancy, can be seen in association with other autoimmune diseases. Complete villous atrophy is associated with a severe inflammatory reaction on small bowel biopsies. Although some cases remit after an extended period of time, most patients die without immunosuppressive therapy, which can include 6-MP drug therapy.

Eosinophilic gastrointestinal disease, including eosinophilic gastroenteritis and eosinophilic enteropathy, is characterized by a dense infiltration of eosinophils in one or more areas of the gastrointestinal tract, variable intestinal symptoms, and usually a peripheral eosinophilia (80% of cases). Food allergic, including allergic gastrointestinal disease, and eosinophilic disorders of the gastrointestinal tract are commonly treated by dietary elimination of the offending nutrients. However, both food induced and eosinophilic enteropathies may, in certain circumstances, require corticosteroid and immunosuppressive therapy, including 6-MP (Russo et al., *Pediatric Dev. Path.* 2:65–71 (1999)).

The methods of the invention relate to optimizing therapeutic efficacy of 6-MP drug treatment of an immune-mediated GI disorder, including IBD such as Crohn's disease and ulcerative colitis and subtypes thereof. The methods of the invention are particularly useful for treating patients dependent on steroid therapy for maintenance of remission of disease in Crohn's disease and ulcerative colitis patients. As used herein, the phrase "optimizing therapeutic efficacy of 6-MP drug treatment" refers to adjusting the therapeutic dosage of a 6-MP drug such as 6-MP or azathioprine so that the concentration of a 6-MP metabolite that is correlated with effective treatment is maintained. As set forth above, the methods of the invention allow the clinician to provide an individually optimized dosage of a 6-MP drug so as to achieve a target level of a 6-MP metabolite in a particular patient, thereby optimizing the effectiveness of 6-MP drug therapy in the patient. Therapeutic efficacy generally is indicated by alleviation of one or more signs or symptoms associated with the disease. In the case of immune-mediated GI disorders, in particular IBD, therapeutic efficacy is indicated by alleviation of one or more signs or symptoms associated with the disease, including, for example, joint pain, arthritis, arthalgia, anorexia, growth failure, fistula closure, abdominal pain, diarrhea, recurrent fever, anemia, weight loss, rectal bleeding, inflammation of the intestine, and loose discharges of blood, pus and mucus. Methods for determining therapeutic efficacy, in particular for treating IBD, are disclosed herein in Examples I and II.

Therapeutic efficacy can be readily determined by one skilled in the art as the alleviation of one or more signs or symptoms of the disease being treated. In the case of IBD, patients can be analyzed using a Crohn's disease activity index (Best et al., *Gastroenterology* 70:439–444 (1976)). IBD patients can also be analyzed using a Harvey-Bradshaw index (HBI) (Harvey and Bradshaw, *Lancet* 1:514 (1980)). The Harvey-Bradshaw index provides an analytical method for measuring signs or symptoms of Crohn's disease, including the signs or symptoms of general well-being, abdominal pain, number of liquid stools per day, abdominal mass, and complications such as arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula and abscess. The Harvey-Bradshaw index is particularly useful when evaluating pediatric patients.

Previous studies suggested that measurement of 6-MP metabolite levels can be used to predict clinical efficacy and tolerance to azathioprine or 6-MP (Cuffari et al., *Gut* 39:401–406 (1996a)). However, it was unknown what concentrations of 6-MP metabolites correlated with optimized therapeutic efficacy or with toxicity (Cuffari et al., supra, 1996a). As disclosed herein, levels of 6-MP metabolites such as 6-TG and 6-MMP were determined and correlated with therapeutic efficacy and toxicity associated with 6-MP drug therapy (see Examples I and II).

The invention is directed to methods of optimizing therapeutic efficacy of 6-MP drug treatment of an immune-mediated GI disorder by monitoring predetermined levels associated with therapeutic efficacy or toxicity and adjusting the 6-MP drug dosage so as to maintain an optimized dose that is efficacious and has reduced toxicity. The methods involve administering a 6-MP drug such as 6-MP or azathioprine to a subject having an immune-mediated GI disorder and determining a level of a 6-MP metabolite in the subject having the immune-mediated GI disorder. The methods of the invention are advantageous in that the dosage of a 6-MP drug can be adjusted to maximize the efficacy of treating an immune-mediated GI disorder such as IBD while minimizing toxicity associated with 6-MP drug treatment.

As used herein, the term "6-mercaptopurine metabolite" refers to a product derived from 6-mercaptopurine in a

biological system. Exemplary 6-mercaptopurine metabolites are shown in FIG. 1 and include 6-thioguanine (6-TG), 6-methyl-mercaptopurine (6-MMP) and 6-thiouric acid and analogues thereof. For example, 6-MP metabolites include 6-TG bases such as 6-TG, 6-thioguanosine mono-, di- and tri-phosphate; 6-MMP bases such as 6-methyl-mercaptopurine and 6-methyl-thioinosine monophosphate; 6-thioxanthosine (6-TX) bases such as 6-thioxanthosine mono-phosphate; 6-thiouric acid (6-TUA); and 6-MP bases such as 6-mercaptopurine and 6-thioinosine monophosphate (see FIG. 2). The immunosuppressive properties of 6-MP are believed to be mediated via the intracellular transformation of 6-MP to its active metabolites such as 6-TG and 6-MMP nucleotides. Furthermore, 6-MP metabolites such as 6-TG and 6-MMP were found to correlate with therapeutic efficacy and toxicity associated with 6-MP drug treatment of IBD patients (see Examples I and II).

The level of a 6-MP metabolite can be determined by methods well known in the art including, for example, those described in Lilleyman and Lennard, *Lancet* 343:1188–1190 (1994); Lennard and Singleton, i J. Chromatography Biomed. Applicat. 583:83–90 (1992); Lennard and Singleton, *J. Chromatography* 661:25–33 (1994); and Cuffari et al., *Can. J. Physiol. Pharmacol.* 74:580–585 (1996b)). 6-MP metabolites such as 6-TG and 6-MMP can be measured, for example, by collecting red blood cells and extracting thiobases, for example, 6-MP, 6-TG, 6-TX and 6-MMP, which are released by acid hydrolysis. 6-MMP is converted to a form extractable by phenyl mercury salts (Dervieux and Boulieu, *Clin. Chem.* 44:2511–2525 (1998); Duchesne et al., *Proc. Amer. Soc. Clin. Oncol.* 13:137 (1994a); Duchesne et al., *Can. J. Physiol. Pharmacol.* 72:197 (1994b)). Such an analysis measures the thiobase and its analogues, including ribonucloside, ribonucleotide, deoxyribonucleoside, deoxyribonucleotide thiobases as well as mono-, di- and tri-phosphate analogues, which have been converted to thiobases.

Acid hydrolyzed extracts can be analyzed by resolving 6-MP metabolites and measuring their levels. For example, HPLC such as reverse phase HPLC is a useful method for resolving and measuring the levels of 6-MP metabolites, including 6-MP, 6-TG and 6-MMP (Lennard and Singleton, supra, 1992). Ultraviolet light (UV) detection can be used to measure the 6-MP metabolites. A particularly useful method of measuring 6-MP metabolites is isocratic reverse phase HPLC with UV detection (Cuffari et al., supra, 1996b).

Other methods for measuring 6-MP metabolites can also be used. For example, ion-pairing HPLC with dual UV-wavelength detection can be used to measure 6-MP metabolites (Zimm and Strong, *Anal. Biochem.* 160:1–6 (1987)). Additional methods for measuring 6-MP metabolites include, for example, capillary electrophoresis with laser-induced fluorescence detection (Rabel et al., *Anal. Biochem.* 224:315–322 (1995)); anion exchange chromatography and fluorescent detection (Tidd and Dedhar *J. Chromatography* 145:237–246 (1978)); lanthanum precipitation, acid hydrolysis, back extraction and fluorometric assay (Fletcher and Maddocks, *Brit. J. Clin. Pharmacol.* 10:287–292 (1980)); thin layer chromatography (Bennet and Allen, *Cancer Res.* 31:152–158 (1971)); precolumn derivatization with the thiol-reactive fluorophore monobromobimane, treatment with alkaline phosphatase, HPLC resolution and quantification by fluorometry (Warren and Slordal, *Anal. Biochem.* 215:278–283 (1993)); and enzymatic hydrolysis followed by HPLC separation and UV detection (Giverhaug et al., *Ther. Drug Monit.* 19:663–668 (1997)). 6-MP metabolites such as 6-TG can also be measured in DNA by degrading DNA to deoxyribonucleosides, derivatizing deoxy-6-TG with a fluorophore and resolving on reverse phase HPLC (Warren et al., *Cancer Res.* 55:1670–1674 (1995)).

As used herein, the level of a 6-MP metabolite can include the 6-MP metabolite itself, or the level of the 6-MP metabolite and analogues thereof. For example, as described above, acid hydrolysis can be used to release thionucleotides from a sample, resulting in conversion of mono-, di- and tri-phosphates to thiobases. In such an analysis, the level of several analogues of a thionucleotide are measured (see FIG. 2). For example, measuring 6-TG can include 6-thioguanosine 5'-mono-, di-, and tri-phosphate, and 6-thiodeoxyguanosine 5'-di-, and tri-phosphate. Measuring 6-MP can include 6-mercaptopurine and 6-thioinosine 5'-monophosphate. Measuring 6-MMP can include 6-methylmercaptopurine and 6-methylthioinosine 5'-monophosphate, and can also include 6-methylthioinosine di- and tri-phosphate, as well as 6-methyl thioguanosine.

A particularly useful determination of the level of a 6-MP metabolite is the median level of the 6-MP metabolite since the distribution of 6-MP metabolite values is trimodal. Unless otherwise designated, the levels referred to herein are median levels. A 6-MP metabolite level can also be a mean level, if so desired. Unless otherwise designated, the levels of 6-MP metabolites referred to herein are values per $8x10^8$ RBC, whether reported as mean or median values.

6-MP metabolite levels can be conveniently assayed using red blood cells because such cells are readily available from the patient, lack a nucleus and are easy to manipulate. However, it should be understood that any measurement that allows determination of 6-MP metabolite levels can be used. For example, leukocytes can be used to measure 6-MP metabolite levels, which can be correlated with 6-MP metabolite levels in erythrocytes (Cuffari et al., supra, 1996b). Regardless of the method employed to measure 6-MP metabolites, one skilled in the art can readily measure 6-MP metabolite levels in a sample, for example, in leukocytes or DNA obtained from a patient, and correlate the level of 6-MP metabolites to the values disclosed herein, which were determined using RBC.

For convenience, levels of 6-MP metabolites disclosed herein are given in terms of an assay with RBC and, therefore, are given as an amount of a 6-MP metabolite in a given number of RBCs. 6-MP metabolites assayed in RBCs can also be determined relative to the amount of hemoglobin. However, it should be understood that one skilled in the art can measure 6-MP metabolite levels in samples other than RBCs and readily correlate such levels with 6-MP metabolite levels in RBCs. For example, one skilled in the art can readily determine levels of a 6-MP metabolite in cells such as leukocytes, or cells from the oral mucosa, and in RBCs by measuring the level of 6-MP metabolites in both types of cells and determining the correspondence between levels of 6-MP metabolites in RBCs and the levels in the other cells. Once a correspondence between 6-MP metabolites in RBCs and in a sample has been determined, one skilled in the art can use that correspondence to measure levels in the other sample and correlate those levels with the levels in RBCs disclosed herein.

As disclosed herein, the level of 6-TG in an IBD patient treated with a 6-MP drug was found to correlate with therapeutic efficacy (see Examples I and II). In particular, a median level of 230 pmol 6-TG/$8x10^8$ RBC or more was found in IBD patients who responded to 6-MP drug therapy.

Thus, as disclosed herein, a level of at least about 230 pmol 6-TG per 8×10^8 RBC can be a minimal therapeutic level of 6-TG for efficaciously treating a patient. Accordingly, a level of 6-TG below about 230 pmol/8×10^8 RBC indicates a need to increase the amount of a 6-MP drug administered to the patient. A minimal therapeutic level of 6-TG for efficaciously treating a patient also can be, for example, at least about 240 pmol per 8×10^8 RBC; at least about 250 pmol per 8×10^8 RBC; at least about 260 pmol per 8×10^8 RBC; at least about 280 mol per 8×10^8 RBC or at least about 300 pmol per 8×10^8 RBC. It is understood that the minimal therapeutic levels of 6-TG disclosed herein are useful for treating immune-mediated gastrointestinal disorders, including IBD, as well as non-IBD autoimmune diseases.

The methods of the invention directed to determining whether a patient has a minimal therapeutic level of a 6-MP metabolite are useful for indicating to the clinician a need to monitor a patient for therapeutic efficacy and to adjust the 6-MP drug dose, as desired. For example, in a patient having less than a minimal therapeutic level of a 6-MP metabolite such as 6-TG and who also presents as unresponsive to 6-MP drug therapy or having poor responsiveness to 6-MP drug therapy as measured by minimal or no effect on a sign or symptom of the disease being treated, one skilled in the art can determine that the dosage of a 6-MP drug should be increased. However, if it is determined that a patient has less than a predetermined minimal therapeutic level of a 6-MP metabolite but is responsive to 6-MP therapy, the current dose of 6-MP drug can be maintained. Based on measuring 6-MP metabolite levels and assessing the responsiveness of the patient to 6-MP therapy, one skilled in the art can determine whether a 6-MP drug dose should be maintained, increased, or decreased.

Although 6-MP drugs such as 6-MP and azathioprine can be used for effective treatment of an immune-mediated GI disorder, including IBDs such as Crohn's disease or ulcerative colitis, administration of such drugs can be associated with toxic side effects. Toxicities associated with 6-MP drug administration include pancreatitis, bone marrow depression, allergic reactions and drug hepatitis as well as neoplasms and infectious complications (Present et al., *Annals Int. Med.* 111:641–649 (1989); Cuffari et al., supra, 1996a). As disclosed herein, various toxicities associated with 6-MP drug treatment, including hepatic toxicity, pancreatic toxicity and hematologic toxicity, correlate with the level of 6-MP metabolites in a subject administered a 6-MP drug (see Examples I and II).

Thus, the present invention also provides a method of reducing toxicity associated with 6-MP drug treatment of an immune-mediated GI disorder. The method of the invention for reducing toxicity associated with 6-MP drug treatment includes the steps of administering a 6-MP drug to a subject having an immune-mediated GI disorder; and determining a level of a 6-MP metabolite in the subject having the immune-mediated GI disorder, where a level of the 6-MP metabolite greater than a predetermined toxic level of the 6-MP metabolite indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP drug treatment of the immune-mediated GI disorder. In a method of the invention, the 6-MP metabolite can be, for example, 6-TG and the predetermined toxic level of 6-TG can correspond, for example, to a level of about 400 pmol per 8×10^8 red blood cells. Where the elevated 6-MP metabolite is 6-TG, the toxicity associated with 6-MP treatment can be, for example, hematologic toxicity, including leukopenia or bone marrow suppression. The 6-MP metabolite also can be a metabolite such as 6-MMP, and the predetermined toxic level of 6-MMP can correspond, for example, to a level of about 7000 pmol per 8×10^8 red blood cells. Where the elevated 6-MP metabolite is 6-MMP, the toxicity associated with 6-MP drug treatment can be, for example, hepatic toxicity.

As disclosed herein, the level of a 6-MP metabolite can be determined in a subject treated with a 6-MP drug and compared to a predetermined toxic level of a 6-MP metabolite such as 6-TG or 6-MMP to adjust future 6-MP drug administration, thereby reducing toxicity in the subject. For example, as disclosed herein, levels of 6-TG above about 400 pmol/8×10^8 RBC indicated that a patient was likely to experience toxicity, in particular hematologic toxicity such as leukopenia (see Examples I and II). Accordingly, a level of 6-TG above about 400 pmol/8×10^8 RBC can be a predetermined toxic level of 6-TG, which indicates that the amount of 6-MP drug subsequently administered should be decreased.

It is understood that, when a patient is determined to have a level of a 6-MP metabolite such as 6-TG or 6-MMP higher than a predetermined toxic level, one skilled in the art can make a determination as to whether a 6-MP drug dose should be decreased. For example, if the level of a 6-MP metabolite such as 6-TG or 6-MMP is higher than a predetermined toxic level, one skilled in the art can monitor for toxic side effects by measuring one or more of the toxicities associated with 6-MP drug treatment, as disclosed herein. As disclosed herein, a level of 6-TG greater than about 400 pmol per 8×10^8 RBCs was associated with increased risk of leukopenia or bone marrow suppression. Therefore, one skilled in the art can measure white blood cells (WBC) in a patient having levels of 6-TG higher than a predetermined toxic level to determine if the patient is exhibiting signs of reduced WBC counts. If such a patient exhibits signs of leukopenia or bone marrow suppression, the 6-MP drug dose can be reduced. However, if it is determined that a patient has levels of a 6-MP metabolite higher than a predetermined toxic level but does not exhibit signs of leukopenia or other 6-MP drug toxicities, one skilled in the art can determine that the current 6-MP drug dose can be maintained. Based on measuring 6-MP metabolite levels and determining signs or symptoms of toxicities associated with 6-MP drug treatment, one skilled in the art can determine whether a 6-MP drug dose should be maintained or decreased. As such, a level of a 6-MP metabolite higher than a predetermined toxic level can indicate a need to measure a toxicity associated with 6-MP drug treatment such as measuring WBCs or any of the other signs or symptoms of toxicities associated with 6-MP drug treatment to determine if the 6-MP drug dose should be adjusted.

Furthermore, it is understood that, when decreasing the 6-MP drug dose, one skilled in the art will know or can readily determine whether the 6-MP drug dose should be decreased to a lower dose or whether 6-MP drug administration should be stopped for some period of time, or terminated. For example, if the clinician determines that 6-MP drug therapy should be stopped for some period of time due to levels of a 6-MP metabolite exceeding a level predetermined to be toxic, the levels of 6-MP metabolites can be monitored after stopping 6-MP drug therapy until the level of the toxic 6-MP metabolite returns to a safe, non-toxic level. At that time, the clinician can resume 6-MP drug therapy, if desired.

The methods of the invention for reducing toxicity associated with 6-MP drug treatment of a disease involve comparing a level of a 6-MP metabolite to a predetermined toxic level of a 6-MP metabolite. In general, a "predetermined

toxic level" of a 6-MP metabolite means a level of a 6-MP metabolite that has been correlated with one or more toxicities associated with 6-MP drug treatment. As disclosed herein, a predetermined toxic level of 6-TG can be about 400 pmol per $8x10^8$ RBC. A predetermined toxic level of 6-TG also can be about 350 pmol per $8x10^8$ RBC; 370 pmol per $8x10^8$ RBC; 390 pmol per $8x10^8$ RBC; 425 pmol per $8x10^8$ RBC; or 450 pmol per $8x10^8$ RBC. It is understood that the predetermined toxic levels of 6-TG disclosed herein are useful for treating immune-mediated GI disorders, including IBD, as well as non-IBD autoimmune diseases.

Another 6-MP metabolite useful for predicting the likelihood of toxicity is 6-methyl-mercaptopurine (6-MMP). As disclosed herein, a level of greater than about 7000 pmol 6-MMP/$8x10^8$ in patients administered a 6-MP drug was associated with toxicity, in particular hepatotoxicity (see Examples I and II). These results indicate that the level of 6-MMP can be used to predict toxicity in a patient treated with a 6-MP drug. As disclosed herein, a predetermined toxic level of 6-MMP can be about 7000 pmol per $8x10^8$ RBC. A predetermined toxic level of 6-MMP also can be about 6000 pmol per $8x10^8$ RBC; 6500 pmol per $8x10^8$ RBC; 7500 pmol per $8x10^8$ RBC; or 8000 pmol per $8x10^8$ RBC. It is understood that the predetermined toxic levels of 6-MMP disclosed herein are useful for treating immune-mediated GI disorders, including IBD, as well as non-IBD autoimmune diseases. According to a method of the invention, if the level of 6-MMP is above a predetermined toxic level, the subsequent administration of a 6-MP drug can be decreased to minimize toxicity.

Further provided by the invention is a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-MP drug treatment of an immune-mediated GI disorder such as IBD. The method includes the steps of administering a 6-MP drug to a subject having an immune-mediated GI disorder; determining a level of 6-TG in the subject having the immune-mediated GI disorder; and determining a level of 6-MMP in the subject having the immune-mediated GI disorder, where a level of 6-TG less than a predetermined minimal therapeutic level indicates a need to increase the amount of 6-MP drug subsequently administered to the subject, thereby increasing therapeutic efficacy; where a level of 6-TG greater than a predetermined toxic level of 6-TG indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP treatment of the immune-mediated GI disorder; and where a level of 6-MMP greater than a predetermined toxic level of 6-MMP indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject, thereby reducing toxicity associated with 6-MP drug treatment of the immune-mediated GI disorder.

In such a method of optimizing therapeutic efficacy and reducing toxicity associated with 6-MP drug treatment of an immune-mediated GI disorder such as IBD, the predetermined minimal therapeutic level of 6-TG can be, for example, a level corresponding to about 230 pmol per $8x10^8$ red blood cells; the predetermined toxic level of 6-TG can be, for example, a level corresponding to about 400 pmol per $8x10^8$ red blood cells; and the predetermined toxic level of 6-MMP can be, for example, a level corresponding to about 7000 pmol per $8x10^8$ red blood cells. In a method of the invention, the subject having an immune-mediated GI disorder such as IBD can be, for example, a pediatric subject. The level of 6-TG and 6-MMP each can be conveniently determined, for example, in red blood cells using HPLC.

The methods of the invention are useful for optimizing the amount of a 6-MP drug to be administered to a patient with an immune-mediated GI disorder such as IBD. By measuring the levels of 6-MP metabolites such as 6-MMP and 6-TG, one skilled in the art can determine the 6-MP drug dosage that will result in optimized therapeutic efficacy and reduced toxicity when administered to a patient.

As disclosed herein, gender and age differences were observed in pediatric patients treated with 6-MP drug therapy (see Example III). Very little change in 6-MP metabolite levels of 6-TG and 6-MMP was seen for girls who had gone through puberty (older than age 12). However, boys who had gone through puberty (older than age 14) had a marked decrease in the level of 6-MMP, suggesting that hormonal changes occurring during puberty can affect the metabolism of a 6-MP drug. Therefore, the methods of the invention can additionally be used to monitor 6-MP metabolite levels in adolescents, particularly those going through puberty, in order to optimize therapeutic efficacy or minimize toxic side effects associated with 6-MP therapy.

As disclosed herein, TPMT genotyping is useful for predicting the effectiveness of 6-MP therapy in an IBD patient (see Example IV). Heterozygote patients are expected to have lower TPMT activity and should therefore be monitored for high levels of 6-TG for possible toxic levels associated with leukopenia or bone marrow suppression. 6-MP drug doses can be reduced accordingly. Wild type homozygous patients are expected to have higher TPMT activity and should therefore be monitored to maintain an effective therapeutic level of 6-TG and to determine if patients develop toxic levels of 6-MMP. Homozygous patients deficient in TPMT activity can be treated with lower doses of a 6-MP drug provided that patients are closely monitored for toxicity such as leukopenia. Therefore, TPMT genotyping can be used to predict patient responsiveness to and potential toxicities associated with 6-MP drug therapy. Furthermore, TPMT genotyping can be combined with other methods of the invention to both determine TPMT genotype and to monitor 6-MP metabolites. TPMT genotyping can be particularly valuable when determining a starting dose of 6-MP drug therapy but can also be useful when adjusting 6-MP drug doses after therapy has begun.

The invention additionally provides a method of optimizing therapeutic efficacy of 6-MP drug treatment of a non-IBD autoimmune disease. The method includes the steps of administering a 6-MP drug to a subject having a non-IBD autoimmune disease; and determining a level of 6-thioguanine (6-TG) in the subject having the non-IBD autoimmune disease, where a level of 6-TG less than a minimal therapeutic level indicates a need to increase the amount of 6-MP drug subsequently administered to the subject and where a level of 6-TG greater than a predetermined toxic level indicates a need to decrease the amount of 6-MP drug subsequently administered to the subject. The level of 6-MMP can also be monitored in a patient having a non-IBD autoimmune disease to determine if the level is higher than a predetermined toxic level of 6-MMP.

The methods of the invention can be used to optimize therapeutic efficacy of 6-MP drug treatment of a non-IBD autoimmune disease. Such a non-IBD autoimmune disease can be any non-IBD autoimmune disease treatable by a 6-MP drug such as 6-MP or azathioprine and, in particular, can be a disease such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune hepatitis (chronic active hepatitis) or pemphigus vulgaris.

As used herein, the term "non-IBD autoimmune disease" means a disease resulting from an immune response against

a self tissue or tissue component, including both self antibody responses and cell-mediated responses. The term non-IBD autoimmune disease encompasses organ-specific non-IBD autoimmune diseases, in which an autoimmune response is directed against a single tissue, including myasthenia gravis, vitiligo, Graves' disease, Hashimoto's disease, Addison's disease, autoimmune gastritis, and Type I diabetes mellitus. The term non-IBD autoimmune disease also encompasses non-organ specific autoimmune diseases, in which an autoimmune response is directed against a component present in several or many organs throughout the body. Non-organ specific autoimmune diseases include, for example, systemic lupus erythematosus, progressive systemic sclerosis and variants, polymyositis and dermatomyositis, and rheumatoid disease. Additional non-IBD autoimmune diseases include pernicious anemia, primary biliary cirrhosis, autoimmune thrombocytopenia, and Sjögren's syndrome. One skilled in the art understands that the methods of the invention can be applied to these or other non-IBD autoimmune diseases treatable by a 6-MP drug such as 6-MP or azathioprine, or other 6-MP drugs, as desired. Specifically excluded from the term "non-IBD autoimmune disease" are diseases resulting from a graft versus host response and inflammatory bowel diseases such as Crohn's disease or ulcerative colitis.

The methods of the invention are also useful for treating a non-immune-mediated GI disorder autoimmune disease. As used herein, the term "non-immune-mediated GI disorder autoimmune disease" is a non-IBD autoimmune disease and specifically excludes immune-mediated GI disorders.

The methods of the invention can be particularly useful for optimizing therapeutic efficacy of 6-MP drug treatment of rheumatoid arthritis. Rheumatoid arthritis is a chronic systemic disease primarily of the joints, usually polyarticular, marked by inflammatory changes in the synovial membranes and articular structures and by muscle atrophy and rarefaction of the bones.

The methods of the invention also can be particularly valuable for optimizing therapeutic efficacy of 6-MP drug treatment of lupus erythematosus and, in particular, systemic lupus erythematosus (SLE). Systemic lupus erythematosus is a chronic, remitting, relapsing inflammatory, and sometimes febrile multisystemic disorder of connective tissue. SLE can be acute or insidious at onset and is characterized principally by involvement of the skin, joints, kidneys and serosal membranes.

Autoimmune hepatitis, also called chronic active hepatitis, also can be treated with a 6-MP drug and the dose optimized using the methods of the invention. Autoimmune hepatitis is a chronic inflammation of the liver occurring as a sequel to hepatitis B or non-A, non-B hepatitis and is characterized by infiltration of portal areas by plasma cells and macrophages, piecemeal necrosis, and fibrosis.

The methods of the invention also can be useful for treating pemphigus vulgaris, the most common and severe form of pemphigus, which is a chronic, relapsing and sometimes fatal skin disease characterized clinically by the development of successive crops of vesicles and bullae and treated by azathioprine. This disorder is characterized histologically by acantholysis, and immunologically by serum autoantibodies against antigens in the intracellular zones of the epidermis.

The methods of the invention can also be used to optimize the therapeutic efficacy of 6-MP drug treatment of graft versus host disease, which can occur in transplant patients. Graft versus host disease occurs when a transplant patient has an immune reaction to the non-self transplant organ or tissue. The methods of the invention for optimizing the therapeutic efficacy of 6-MP drug treatment is particularly useful for treating heart, kidney and liver transplant recipients. The methods of the invention can be used to optimize therapeutic efficacy and/or minimize toxicity associated with 6-MP drug treatment of a transplant patient.

The following examples are intended to illustrate but not limit the present invention.

EXAMPLE I

6-Mercaptopurine Metabolite Levels Predict Clinical Efficacy and Drug Toxicity in Pediatric IBD

This example describes measuring 6-MP metabolite levels and correlation with the response of IBD patients treated with a 6-MP drug.

The levels of the 6-MP metabolites 6-TG and 6-MMP were measured in IBD patients to whom 6-MP pro-drug was administered, and the relationship of 6-MP metabolites to clinical disease activity and drug toxicity was determined. Briefly, blood was sampled (n=89) prior to daily administration of 6-MP in 55 IBD patients (CD n=51, UC n=4) receiving 1–1.5 mg/kg/day over at least a 4 month period (≧4 mo.). When AZA was administered, a conversion factor of 2.07 was used to convert to the equivalent 6-MP dose. Twice as much AZA is administered relative to 6-MP to have an equivalent dose of 6-MP.

Erythrocyte 6-TG, 6-MMP and 6-MP thiobases were measured (pmol/8x10^8 RBC) using reverse phase HPLC. Briefly, blood samples were collected in EDTA (ethylene diamine tetraacetic acid) as anticoagulant. Cells were centrifuged and washed three times with an equal volume of 0.9% saline. Washed packed cells were stored at −70° C. until analysis was performed.

For acid hydrolysis, 500 μl deionized H_2O, 50 μl thawed red blood cells, 40 μl of the appropriate standard or control, 500 μl 3.0 N H_2SO_4, and 300 μl 10 mM dithiothreitol (DTT) was added to an 8 ml glass screw cap tube. The capped tubes were placed in a heating block preheated to 100° C. and hydrolyzed. For 6-MMP, hydrolysis was carried out for 5 hours. For 6-MP and 6-TG, hydrolysis was carried out for 1 hour. After the incubation, tubes were cooled in a room temperature water bath. To tubes hydrolyzed for 5 hours (6-MMP), 400 μl 3.4 N NaOH and 1.0 ml 2 M Tris buffer, pH 9.0 was added. To tubes hydrolyzed for 1 hour (6-MP/6-TG), 450 μl 3.4 N NaOH and 500 μl 2M Tris base was added. A volume of 4 ml 0.03% phenylmercuric chloride in methylene chloride was added to each tube. The tubes were capped and lightly agitated on a bi-directional rotator (15 min for 6-MMP and 30 min for 6-MP/6-TG). The contents were transferred to a 15 ml polypropylene centrifuge tube and centrifuged at 3500 rpm for 3 min at 10° C. The aqueous phase (top layer) was discarded, and 3.0 ml of the organic phase (bottom layer) was transferred to a clean 15 ml polypropylene centrifuge tube. The analytes in the organic phase were back extracted by adding 225 μl 0.1 N HCl and lightly mixing on an orbital rotator for 5 min. Following vortexing for 30 seconds, the tubes were centrifuged at 3500 rpm for 3 min at 10° C.

For 6-MMP analysis, 50 μl analyte was analyzed on a C18 reverse phase column with the mobile phase containing 1 mM DTT, 2.078% triethylamine and 4% methanol, adjusted to pH 3.2 with concentrated H_3PO_4. For 6-MP and 6-TG analysis, 100 μl analyte was analyzed on a C18 reverse

phase column using 0.1 M H_3PO_4 and 1 mM DTT in H_2O as the mobile phase.

Hepatic, pancreatic and hematological tests were obtained every 3 months. Clinical remission was defined as a Harvey Bradshaw Index <5 in those patients off corticosteroids or weaned to a level of prednisone ≦0.4 mg/kg/od (administered every other day). Treatment failures were defined as non-responders (HBI >5 or steroid dependence) or cessation of 6-MP due to side effects.

As shown in Table 1, a 6-TG level of >225 pmol per $8x10^8$ RBC was associated with remission. The median values shown in the tables represent pmol of the indicated 6-MP metabolite per $8x10^8$ RBC. Excessive 6-TG and 6-MMP levels were associated with leukopenia and hepatotoxicity, respectively. Negligible metabolite levels detected non-compliance as a cause of treatment failure in 2/31 cases. These results indicate that 6-MP metabolite levels predict both clinical responsiveness and drug-related toxicity.

TABLE 1

Group	n	median 6-TG	6-TG >225	median 6-MMP
Responders	58	295	45/58 (78%)	3094
Non-responders	31	184*	8/31 (26%)	2548
Hepatic toxicity	7	258	5/7	9211**
Pancreatic toxicity	6	211	2/6	2342
Hematologic toxicity	6	414◇	5/6	7042
p Values		* < 0.001 ◇ < 0.03	‡ 0 < 0.001	** < 0.001

These results demonstrate that determining levels of 6-MP metabolites is useful for predicting efficacy and toxicity of 6-MP drug therapy administered to IBD patients.

EXAMPLE II

6-Mercaptopurine Metabolite Levels Correlate with Optimal 6-MP Therapy in IBD Patients

This example describes prospective examination of the correlation of 6-MP metabolite levels with therapeutic response to 6-MP drug therapy and 6-MP drug related toxicity in IBD patients treated with 6-MP.

To obtain additional statistical data on IBD patients treated with a 6-MP drug, additional patients and samples were analyzed and combined with the data obtained in Example I. Blood was sampled at least once in 93 IBD patients followed at Sainte-Justine Hospital IBD Center, Montreal, Canada, who were administered 6-MP drug therapy for at least 4 months. The 93 patients were pediatric patients, with 80 diagnosed as having CD, 8 diagnosed as having UC, and 5 diagnosed as having indeterminate colitis (CD or UC). All but 7 patients were given AZA. The dosages were converted to 6-MP equivalents using a factor of 2.07 as described in Example I. For some patients, two or more samples were obtained and analyzed. Response to 6-MP was defined by clinical remission (HBI <5, closed fistula) without corticosteroids. Disease activity and physical exam were ascertained at each clinic visit at which 6-MP metabolite levels were determined (clinical evaluation point). Hematological, pancreatic and hepatic laboratory parameters were evaluated simultaneously. Erythrocyte 6-TG and 6-MMP concentrations (pmol/$8x10^8$ RBC) were measured by HPLC (Cuffari et al., supra, 1996a).

The results of the analysis of 6-MP metabolites in IBD patients are shown in Table 2. The number of samples corresponds to the number of different samples obtained from the 93 patients. 6-TG quartile analysis, in which values are determined at 25, 50 and 75% of the data set, revealed that the frequency of response significantly increased at levels >230 pmol/$8x10^8$ RBC ($p < 0.01$). Among patients in relapse, only 28% of patients had 6-TG levels >230 pmol/$8x10^8$ RBC. In contrast, 65% of patients in remission had 6-TG levels >230 pmol/$8x10^8$ RBC ($p<0.01$). Therefore, erythrocyte 6-TG concentrations were significantly and independently associated with therapeutic response to 6-MP drug therapy.

The induction and maintenance of remission was found to be optimal at 6-TG levels >230 pmol/$8x10^8$ RBC. 78% of patients above a median 6-TG of 230 pmol/$8x10^8$ RBC were responders (see FIG. 3). These results indicate that a 6-TG value of 230 pmol/$8x10^8$ RBC can be used to predict efficacy of drug treatment with a 6-MP drug such as 6-MP or azathioprine.

TABLE 2

Clinical evaluation point	(n)	Median 6-TG	Median 6-MMP	Median dose (mg/kg/day)
Remission	106	309*	2600	1.3
Relapse	72	197	1602	1.25
*p value		<0.0001	0.3	0.4

Toxicity in the IBD patients treated with a 6-MP drug was also evaluated. Toxicity was measured essentially as described previously (Cuffari et al., supra, 1996a). Thirty six patients (39%) experienced an adverse event. Hepatotoxicity was observed in 17% of patients, measured as the serum level of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (ALT, AST; exceeding or greater than 2x upper limit of normal). Leukopenia was observed in 14% of patients (white blood cell (WBC) <4000). Pancreatic toxicity was observed in 7% of patients (lipase/amylase >2×N). High 6-MMP levels correlated significantly with hepatotoxicity (5463 with hepatotoxicity versus 2177 without hepatotoxicity; p=0.04). Leukopenia was observed in only 8% (8/106) of samples from patients in remission, with significantly higher 6-TG levels observed in these patients (mean value of 490 in patients with leukopenia versus mean value of 323 without leukopenia; $p<0.04$; median values were 342 versus 307, respectively). Therefore, leukopenia did not correlate with therapeutic efficacy. Furthermore, drug dose (per kg) did not correlate with therapeutic efficacy (see Table 2). However, those patients who do develop leukopenia have a higher 6-TG level than the rest of the responder group. These results indicate that 6-TG levels should be monitored to avoid potential clinical bone marrow suppression in responder patients who have high levels of 6-TG.

These results demonstrate a significant correlation between erythrocyte 6-TG levels and the therapeutic response to 6-MP drug treatment in IBD patients. The induction and maintenance of remission was found to be optimal at 6-TG levels >230 pmol/$8x10^8$ RBC. Therefore, monitoring 6-MP metabolite levels, in particular 6-TG, is useful for determining that a therapeutically effective concentration of 6-MP metabolites is maintained while treating IBD patients with a 6-MP drug. Monitoring 6-MP metabolite levels, in particular 6-TG and 6-MMP, is also useful for minimizing 6-MP drug related toxicity.

EXAMPLE III

Gender and Age Differences in Metabolism of a 6-MP Drug

This example describes gender and age differences observed in pediatric patients treated with 6-MP drug therapy.

Pediatric IBD patients undergoing 6-MP drug therapy were assessed for levels of 6-MP metabolites. These patients were wild type for TPMT. Patients were assessed based on gender and age as it relates to puberty. Puberty is established at 12 years of age in girls and 14 years of age in boys.

As shown in Table 3, the 6-MMP values are much lower in boys after puberty (greater than 14 years). Since the total amount of thiometabolites is lower, this indicates that either lower doses of 6-MP are used or that there is a difference in the bioavailability of 6-MP after puberty in males.

TABLE 3

6-MP Metabolite Levels in Pediatric IBD Patients

	Number Observed	6-TG level (pmol per 8×10^8 RBC)	6-MMP level (pmol per 8×10^8 RBC)	Ratio 6-MMP/ 6-TG
Girls (0–12y)	39	182.2	3447.0	18.52
Girls (>12y)	116	217.2	3304.5	12.55
Boys (0–14y)	51	239.0	3681.6	17.24
Boys (>14y)	104	222.5	1662.3*	6.78*

*$p < 0.001$

These results demonstrate that gender and age can affect the metabolism of 6-MP in pediatric IBD patients undergoing 6-MP drug therapy.

EXAMPLE IV

Thiopurine Methyltransferase (TPMT) Genotyping and Responsiveness to 6-MP Drug Therapy

This example describes TPMT genotyping of IBD patients treated with 6-MP drug therapy.

The genotype of TPMT was determined in IBD patients that were responders and non responders. Genotyping of TPMT was measured essentially as described previously (Baccichet et al., *Leuk. Res.* 21:817–823 (1997); Ziettkiewicz et al., *Gene* 205:161–171 (1997)). The data shown in Table 4 indicate that patients heterozygous for the TPMT mutation had significantly higher 6-TG levels compared to those patients without the mutation. All heterozygote patients were responders to 6-MP.

TABLE 4

TPMT Genotyping of IBD Patients

	Heterozygote	Normal
Responder	100%	55%
Non responder	0%	45%
mean 6-TG	589*	247

p value *less than 0.0001

TPMT genotyping revealed that 8 of 93 (9%) of patients were heterozygotes. No homozygous TPMT deficient patients were detected. All 8 heterozygotes responded to 6-MP and had 6-TG levels >230 pmol/8×10^8 RBC.

These results demonstrate that TPMT genotyping is useful for predicting the effectiveness of 6-MP therapy in an IBD patient. Heterozygote patients are expected to have lower TPMT activity and should therefore be monitored for high levels of 6-TG for possible toxic levels associated with leukopenia or bone marrow suppression. 6-MP drug doses can be reduced accordingly. Wild type homozygous patients are expected to have higher TPMT activity and should therefore be monitored to maintain an effective therapeutic level of 6-TG and to determine if patients develop toxic levels of 6-MMP. Homozygous patients deficient in TPMT activity can be treated with lower doses of a 6-MP drug provided that patients are closely monitored for toxicity such as leukopenia.

All journal articles and references provided herein, in parenthesis or otherwise, are incorporated herein by reference.

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the claims.

We claim:

1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining a level of 6-thioguanine or 6-methylmercaptopurine in said subject having said immune-mediated gastrointestinal disorder,

wherein a level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein a level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or a level of 6-methylmercaptopurine greater than about 7000 pmol per 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

2. The method of claim 1, wherein said immune-mediated gastrointestinal disorder is inflammatory bowel disease (IBD).

3. The method of claim 2, wherein said subject having IBD is a pediatric subject.

4. The method of claim 1, wherein said immune-mediated gastrointestinal disorder is selected from the group consisting of lymphocytic colitis, microscopic colitis, collagenous colitis, autoimmune enteropathy, allergic gastrointestinal disease and eosinophilic gastrointestinal disease.

5. The method of claim 1, wherein said level of 6-thioguanine is determined in red blood cells.

6. The method of claim 5, wherein said level is determined using high pressure liquid chromatography.

7. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising determining the level of 6-thioguanine or 6-methylmercaptopurine in a subject administered a drug providing 6-thioguanine, said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject, and wherein the level of

6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject wherein said decrease reduces toxicity.

8. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is IBD.

9. The method of claim 8, wherein said subject having IBD is a pediatric subject.

10. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is lymphocytic colitis.

11. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is microscopic colitis.

12. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is collagenous colitis.

13. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is autoimmune enteropathy.

14. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is allergic gastrointestinal disease.

15. The method of claim 7, wherein said immune-mediated gastrointestinal disorder is eosinophilic gastrointestinal disease.

16. The method of claim 7, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

17. The method of claim 16, wherein said level is determined using high pressure liquid chromatography.

18. The method of claim 7, wherein said toxicity is hepatic toxicity.

19. The method of claim 7, wherein said toxicity is hematologic toxicity.

20. The method of claim 7, wherein said drug is 6 -mercaptopurine.

21. The method of claim 7, wherein said drug is azathioprine.

22. The method of claim 7, wherein said drug is 6-thioguanine.

23. The method of claim 7, wherein said drug is 6-methylmercaptopurine riboside.

24. A method of optimizing therapeutic efficacy for treatment of an autoimmune disease, comprising determining the level of 6-thioguanine or 6-methyl-mercaptopurine in a subject administered a drug providing 6-thioguanine, said subject having said autoimmune disease,

wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject, and wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject wherein said decrease reduces toxicity.

25. The method of claim 24, wherein said level of 6-thioguanine and said level of 6-methyl-mercaptopurine each is determined in red blood cells.

26. The method of claim 25, wherein said level is determined using high pressure liquid chromatography.

27. The method of claim 24, wherein said toxicity is hepatic toxicity.

28. The method of claim 24, wherein said toxicity is hematologic toxicity.

29. The method of claim 24, wherein said drug is 6 -mercaptopurine.

30. The method of claim 24, wherein said drug is azathioprine.

31. The method of claim 24, wherein said drug is 6-thioguanine.

32. The method of claim 24, wherein said drug is 6 -methylmercaptopurine riboside.

* * * * *

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Test Results

SAMPLE REPORT

PRO-Predict® Metabolites‡

Azathioprine and 6-MP metabolite monitoring

Patient & Order Information

Order ID	419585		
Patient	Test, Patient		
DOB	01/10/1900		
SSN	123-45-6789	Sex	M
Institution ID		Prometheus ID	21740
Ordered	09/04/2003	Completed	09/04/2003
Ordered By	Example Physician M.D.		
ICD9 Codes	780.00		

Report Recipient

Example Physician M.D.
Prometheus Laboratories Inc.
5739 Pacific Center Blvd
Suite 123
San Diego, CA 92121
USA

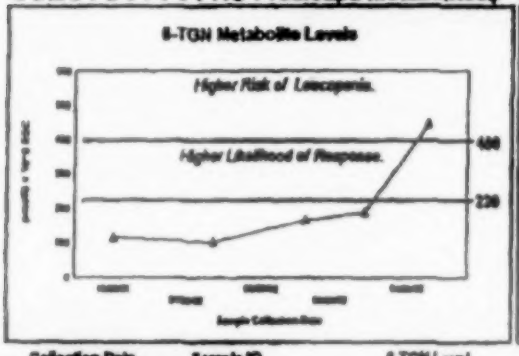
858/824-0695 Phone 858/824-0698 Fax

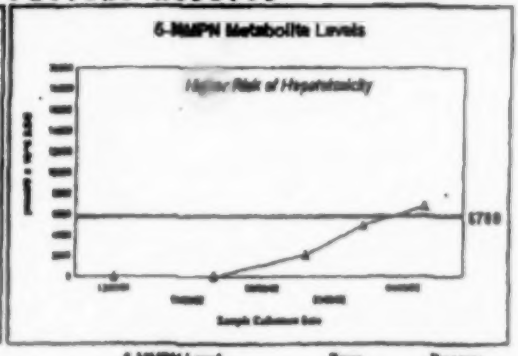
Sample ID: SZ10000004 Collection Date: 04/12/2002 9:33AM (Whole Blood) Institution Sample ID:

Test Results

Metabolite	Result (Units: pmole/8 x 10^6 RBC)	Reference Range	Result Assessment
6-TGN	448	230-400	Higher Risk of Leucopenia. Higher Likelihood of Response.
6-MMPN	6720	< 5700	Higher Risk of Hepatotoxicity.

Cumulative PRO-Predict® Metabolites‡ Patient Results





Collection Date	Sample ID	6-TGN Level	6-MMPN Level	Drug	Dosage
04/12/2002 09:33 AM	SZ10000004	448	6720	Isoxene	150 mg/day
03/17/2002 10:41 AM	SZ10000003	188	4600	Isoxene	100 mg/day
02/21/2002 09:57 AM	SZ10000002	186	2991	Azathioprine	100 mg/day
01/14/2002 11:21 AM	SZ10000001	182	< the lower limit of detection (301)	Azathioprine	75 mg/day
12/08/2001 10:58 AM	SA10000000	116	< the lower limit of detection (301)	Azathioprine	50 mg/day

‡ Patented Technology by Prometheus Laboratories Inc. The therapeutic range and toxic thresholds were established in an IBD patient population receiving azathioprine or 6-mercaptopurine. Metabolite testing should not replace laboratory monitoring for toxicity.

Previous PRO-Predict® TPMT Patient Test Results.

Test Name	Collection Date	Report Date	Sample ID	Result	Interpretation
PRO-Predict® TPMT	01/04/2001	05/16/2003	SC01050042	TPMT*1/TPMT*1	Normal

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Edward R. Wiseman Jr, M.D., Associate Director
Bernard Chang M.D., Associate Director

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    - IBD FIRST STEP™
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    - Celiac Disease Serology
    - Serum Infliximab Measurement
    - HACA Assessment
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    - FIBROSpect™
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    - RA Diagnostic Panel
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PRO-PredictRx® Metabolites

Related Materials: IMURAN® Prescribing Information; Clinical Importance of Metabolite Monitoring

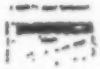
Individualize IMURAN (azathioprine) and 6-MP therapies with PRO-PredictRx testing

PRO-PredictRx® Metabolites

- A test used during treatment for the ongoing evaluation of patient response to AZA/6-MP therapy, so therapeutic adjustments can be made.
- Monitors patients on AZA/6-MP therapy by measuring blood levels of:
  - 6-TGN*, the therapeutically active metabolite that may be associated with leukopenia at high levels
  - 6-MMPN**, a metabolite that may be associated with hepatotoxicity at high levels[7]
- Assists in balancing therapeutic response with possible toxicity.[illegible]
- Enables physicians to tailor dosage levels to a patient's individual metabolism.
- Confirms patient adherence to therapy.[illegible]

AZA Metabolism

Measure Metabolites



Click here for IMURAN safety information

* 6-Thioguanine Nucleotide
** 6-Methylmercaptopurine Nucleotide

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6-MMPN and Metabolites Measuremen Click here...

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Mayo Clinic [redacted] Department of Laboratory Medicine and Pathology [redacted] Rochester, MN 55905

Laboratory Test Abstract Form

Date: 3/10/2004 Laboratory Biochemical Genetics Consultant: Dr. John O'Brien
Unit Code: Supervisor: Paul Cherrick

New Abstract: Secretary: Ms. Annie Pittman

Laboratory Test Abstract Purpose:
Used to facilitate communication among colleagues, serve as one form of peer review, and serve as the information source for MayoAccess and the *Laboratory Medicine eBulletin.*

New test: E-mail draft of Abstract to Medical Editor, Dr. Jane Dale.

Published Name: Azathioprine metabolites profile, blood

Reporting Name: 6-TGN and 6-MMP

Methodology (Brief Method Name): HPLC with UV detection.

Reference Values: Target therapeutic range: 6-TGN>235 pmol/8 X 10^8 cells
Possible myelosuppression: 6-TGN450-700 pmol/8 X 10^8 cells
Possible hepatotoxic level: 6-MMP>5700 pmol/8 X 10^8 cells

Clinical Information:

Azathioprine (Imuran) is the prodrug for 6-mercaptopurine (6-MP) a thio- analogue of purine. 6-MP functions as an antimetabolite of guanine in DNA and RNA synthesis and is an effective immunosuppressive agent used to treat a variety of disorders (e.g., organ transplant rejection, inflammatory bowel disease such as Crohns disease, dermatologic disorders) and to treat some hematologic malignancies (e.g., acute lymphoblastic leukemia).

6-mercaptopurine is also metabolized to 6-methylmercaptopurine (6-MMP) by an alternate detoxification pathway by the methylation enzyme thiopurine methyltransferase (TPMT). TPMT deficiency is inherited in an autosomal recessive fashion. TPMT activity is quite variable across the population. Decreased TPMT activity, particularly in patients homozygous for activity mutations, results in high levels of 6-TGN and azathioprine-related toxicity that may preclude the use of the drug (1). Bone marrow suppression (neutropenia) is the most significant toxic side-effect. Since TPMT deficiency leads to exaggerated toxicity, TPMT should be analyzed prior to dosing patients to determine their eligibility to use this drug. (TPMT analysis is offered by the Mayo laboratories-Test # 80291).The level of 6-MMP is determined using Mayo's new assay but it serves more as a surrogate for TPMT activity since TPMT deficient patients have low levels of 6-MMP and high levels of 6-TGNs. Values of 6-MMP over 5700 pmole/8x10^8 rbc may be associated with hepatotoxicity.

The 6-TGNs are responsible for the immunosuppressive activity and myelotoxicity of azathioprine. Failure of azathioprine therapy is most often due to patients not attaining their therapeutic dose. A decrease in white blood cell count without overt leucopenia is often expected in patients who do achieve successful remission of inflammatory bowl disease. After administration of azathioprine, it is essential to monitor white cell counts to detect myelotoxicity and useful to monitor TGN concentrations. In most adult patients, 6-TGns greater than 235 pmole/8x10^8 rbc (2)

should be attained for remission to occur. A clearly defined toxic level has not been established and may depend on the use and patient population. Overt neutropenia may become evident when TGN levels are between 450 and 750 pmole/8x10^8 rbc. However, some patients who achieved remission have levels of TGNs over 700 pmole/8x10^8 rbc during the course of their therapy but do not have clinically significant myelotoxicity (3). Toxicity established by routine CBC should suggest lowering or withdrawal of the drug without regard to the specific TGN level

Useful For: Monitoring azathioprine therapy

Interpretation: Patients with low concentrations of 6-TGN are at a high risk for disease relapse. In adult inflammatory bowel patients, remission is associated with 6-TGN levels greater than 250 pmol/ 8 X10^8 cells.
Interindividual variability of toxic levels of 6-TGN exist such that values greater than 450 pmol/8 X 10^8 cells may be associated with increased risk of myelosuppression, liver injury, pancreatitis, and allergic reactions. However, values of over 700 have been reported in patients successfully treated (3). White cell count remains the true measure of myelotoxicity.

6-MMP levels of >5700 pmol/8 X 10^8 RBC have been reported to be associated with an increased frequency of abnormal liver function tests.(2)

Cautions:

Patients' blood cell counts should also be monitored during treatment.

Response values were derived mainly from an adult inflammatory bowel disease population.

Supportive Data: See Clinical References

Clinical References:

1) Lennard L, Van Loon JA Weinshilboum RM. Pharmacogenetics of acute azathioprine toxicity: relationship to thiopurine methyltransferase genetic polymorphisms. Clin. Pharmacol Ther 1989 46:149-54.
2) Bloomfield R S, Onken J E. Mercaptopurine metabolite results in clinical gastroenterology practice. Aliment Pharmacol Ther. 2003 17:69-73.
3) Cuffari C, Hunt S, Bayless T, Utilization of erythrocyte 6-thioguanine metabolite levels to optimize azathioprine therapy in patients with inflammatory bowel disease. Gut. 2001 48:642-6
Related references:
Mardini Houssam E, Arnold George L. Utility of measuring 6-methylmercaptopurine and 6-thioguanine nucleotide levels in managing inflammatory bowel disease patients treated with 6-mercaptopurine in a clinical practice setting. J Clin Gastroenterol. 2003 May-Jun; 36(5):390-5.
Relling Mary V, Hancock Michael L, Rivera Gaston K, Sandlund John T, Ribeiro Raul C, Krynetski Evgenie Y, Pui Ching-Hon, Evans William E. Mercaptopurine therapy intolerance and heterozygosity at the thiopurine *S* methyltransferase gene locus. J Natl. Cancer Inst. 1999 Dec 1; 91(23):2001-8.
Dubinsky Marla, Lamothe Stephanie, Yang Hui Ying, Targan Stephan R, Sinnett Daniel,

Memo

Mayo Medical Laboratories
Stabile Building
150 Third Street SW
Rochester, Minnesota 55902
800-533-1710

Implementation Notice: New Test

Date: June 9, 2004
Test Title: Azathioprine Metabolites Profile, Blood
Test Code#: 83306
Effective Date: June 22, 2004

Useful For: Monitoring azathioprine therapy. Azathioprine is converted to 6-mercaptopurine and then to 6-thioguanine nucleotides (6-TGN) in the liver. The 6-TGN are responsible for the immunosuppressive activity and toxicity of azathioprine. 6-mercaptopurine also is metabolized to 6-methylmercaptopurine (6-MMP) by an alternate pathway utilizing the enzyme thiopurine methyltransferase (TPMT).

NOTE: This test replaces test 91338, PRO-Predict Metabolites (thiopurine therapy), currently being referred to Prometheus. 91338 will become obsolete on July 5, 2004. Thiopurine Methyltransferase (TPMT), Erythrocytes is also available as Mayo test 80291.

Methodology: High Performance Liquid Chromatography (HPLC) with UV detection
Reference Range:

6-TGN	>235 pmol/8X10(8)	Therapeutic Range
	>450 pmol/8X10(8)	Possible Myelosuppression
6-MMP	>5700 pmol/8X10(8)	Possible Hepatotoxic

Interpretation: Patients with low values of 6-TGN are at a high risk for disease relapse. Remission is associated with 6-TGN levels greater than 235 pmol/8X10(8) cells. Levels of 6-TGN greater than 450 pmol/8X10(8) cells have been associated with increased risk of myelosuppression, liver injury, pancreatitis, and allergic reactions.

6-MMP levels of >5700 pmol/8X10(8) RBC have been reported to be associated with an increased frequency of abnormal liver function tests.

Specimen Requirement:
Draw blood in a lavender-top (EDTA) tube(s) and send 5.0 mL of whole blood refrigerated. SPECIMEN CANNOT BE FROZEN.

Day Set-up:	Monday through Friday
Analytic Time:	2 Days
List Fee:	$193.50
CPT Code:	80299x2

Questions: Contact your Regional Manager
John O'Brien, PhD, Co-Director, Biochemical Genetics Laboratory
Paul Cleveick, Supervisor, Biochemical Genetics Laboratory
Debie Novak, MML Technical Support

Log on to www.mayomedicalservices.org/html/mml-test-setup.asp or contact MML Telecommunications for test set-up information.

5/27/05 DATE OF MAILING

29

EXHIBIT

ANN M. HOLLAND

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EXHIBIT 5
PAGE 000619

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Attorneys for Plaintiff Prometheus Laboratories Inc.

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

PROMETHEUS LABORATORIES, INC.,

Plaintiff,

v.

MAYO COLLABORATIVE SERVICES dba MAYO MEDICAL LABORATORIES, and MAYO CLINIC ROCHESTER

Defendant.

MAYO COLLABORATIVE SERVICES dba MAYO MEDICAL LABORATORIES,

Counter-Claimant,

v.

PROMETHEUS LABORATORIES, INC.,

Counter-Defendant.

CASE NO.: 04-CV-1200 JAH (RBB)

PROMETHEUS LABORATORIES INC.'S SECOND SUPPLEMENTAL DISCLOSURES PURSUANT TO CASE MANAGEMENT CONFERENCE ORDER REGULATING DISCOVERY AND OTHER PRETRIAL PROCEEDINGS

A. **Disclosure 2(a): Each claim of each patent in suit that is infringed by each opposing party.**

For defendant Mayo Collaborative Services dba Mayo Medical Laboratories ("Mayo"), this disclosure is provided in Attachment A. For defendant Mayo Clinic Rochester, this disclosure is provided in Attachment B.

ATTACHMENT A

Prometheus' Disclosures Pursuant to Case Management Conference Order Items 2(a)-(c), (e) for defendant Mayo

Accused Instrumentality: Offer for sale of Test Code# 83306, entitled "Azathioprine Metabolites Profile, Blood," described in "Implementation Notice: New Test" dated June 9, 2004 from Mayo (hereinafter, "Mayo's Test)."	
U.S. Patent No. 6,355,623 **All Claims Have a Priority Date of September 24, 1998**	
Claim 1 – Literal infringement of all elements	
1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:	Mayo's Test, offered for sale on June 9, 2004, is for "[m]onitoring azathioprine therapy" in patients. Azathioprine "is converted to 6-thioguanine nucleotides in the liver." Mayo's Test was designed for and offered to physicians who treat patients with immune-mediated gastrointestinal disorders (including inflammatory bowel disease) using azathioprine. [*See* Implementation Notice.]
(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and	
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,	The Implementation Notice for Mayo's Test states that it provides physicians with the level of 6-TGN in a patient's blood using High Performance Liquid Chromatography. These patients have immune-mediated gastrointestinal disorders (including inflammatory bowel disease). [*See* Implementation Notice.]
wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells indicates a need to increase the amount of said	The Implementation Notice for Mayo's Test states that a 6-TGN level greater than 235 pmol/8X10(8) is the "therapeutic range" and

drug subsequently administered to said subject and	that "[r]emission is associated with 6-TGN levels grater that [sic] 235 pmol/8X10(8) cells." Such information informs a physician that the next dose of azathioprine given to the patient should be increased (and thus "indicates a need to increase the amount of said drug subsequently administered to said subject"). [*See* Implementation Notice and Court's Order of November 21, 2005.] The phrase "about 230 pmol per 8 x 10^8" means 230 +/- 15%, or 230 +/- 34 pmol per 8 x 10^8; thus a level of 235 pmol per 8 x 10^8 is within about 230 pmol per 8 x 10^8.
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	The Implementation Notice for Mayo's Test states that a 6-TGN level greater than "450 pmol/8X10(8)" is correlated with "Possible Myelosuppression," and that "[l]evels of 6-TGN greater that [sic] 450 pmol/8X10(8) cells have been associated with increased risk of myelosuppression, liver injury, pancreatitis, and allergic reactions." Such information informs a physician that the next dose of azathioprine given to the patient should be decreased (and thus "indicates a need to decrease the amount of said drug subsequently administered to said subject"). [*See* Implementation Notice and Court's Order of November 21, 2005.] The

	phrase "about 400 pmol per 8 x 10^{8}" means 400 +/- 15%, or 400 +/- 60 pmol per 8 x 10^{8} or 340-460 pmol per 8 x 10^{8}; thus a level of 450 pmol per 8 x 10^{8} is within about 400 pmol per 8 x 10^{8}. [*See* Court's Order of November 21, 2005.]
Claim 6 – Literal infringement of all elements	
6. The method of claim 5, wherein said level is determined using high pressure liquid chromatography.	Mayo's Test uses "High Performance Liquid Chromatography" to determine the level of 6-thioguanine in the patient. High Performance Liquid Chromatography is a synonym for High Pressure Liquid Chromatography. [*See* Implementation Notice.]
Claim 32 – Literal infringement of all elements	
32. The method of claim 1, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.	Mayo's Test is for patients who are on "Azathioprine Therapy," i.e., who have been administered the drug azathioprine. [*See* Implementation Notice.]
Claim 7 – Literal infringement of all elements	
7. A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;	Mayo's Test, offered for sale on June 9, 2004, is for "[m]onitoring azathioprine therapy" in patients. Azathioprine "is converted to 6-thioguanine nucleotides in the liver." Mayo's Test was designed for and offered to physicians who treat patients with immune-mediated gastrointestinal disorders (including inflammatory bowel disease) using azathioprine. [*See* Implementation Notice.]

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and	The Implementation Notice for Mayo's Test states that it provides physicians with the level of 6-TGN in a patient's blood using High Performance Liquid Chromatography. These patients have immune-mediated gastrointestinal disorders (including inflammatory bowel disease). [*See* Implementation Notice.]
(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,	The Implementation Notice for Mayo's Test states that it provides physicians with the level of 6-methylmercaptopurine in a patient's blood using High Performance Liquid Chromatography. These patients have immune-mediated gastrointestinal disorders (including inflammatory bowel disease). [*See* Implementation Notice.]
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells or the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	The Implementation Notice for Mayo's Test states that a 6-TGN level greater than "450 pmol/8X10(8)" is correlated with "Possible Myelosuppression," and that "[l]evels of 6-TGN greater that [sic] 450 pmol/8X10(8) cells have been associated with increased risk of myelosuppression, liver injury, pancreatitis, and allergic reactions." Such information informs a physician that the next dose of azathioprine given to the patient should be decreased (and thus "indicates a need to decrease the amount of said drug subsequently administered to said

	subject"). [*See* Implementation Notice and Court's Order of November 21, 2005.] The phrase "about 400 pmol per 8 x 10^8" means 400 +/- 15%, or 400 +/- 60 pmol per 8 x 10^8 or 340-460 pmol per 8 x 10^8; thus a level of 450 pmol per 8 x 10^8 is within about 400 pmol per 8 x 10^8. [*See* Court's Order of November 21, 2005.]
Claim 14 – Literal infringement of all elements	
14. The method of claim 13, wherein said level is determined using high pressure liquid chromatography.	Mayo's Test uses "High Performance Liquid Chromatography" to determine the level of 6-thioguanine in the patient. High Performance Liquid Chromatography is a synonym for High Pressure Liquid Chromatography. [*See* Implementation Notice.]
Claim 33 – Literal infringement of all elements	
33. The method of claim 7, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.	Mayo's Test is for patients who are on "Azathioprine Therapy," i.e., who have been administered the drug azathioprine. [*See* Implementation Notice.]
Claim 22 – Literal infringement of all elements	
22. A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease, comprising: (a) administering a drug providing 6-thioguanine to a subject having said non-IBD autoimmune disease; and	Mayo's Test, offered for sale on June 9, 2004, is for "[m]onitoring azathioprine therapy" in patients. Azathioprine "is converted to 6-thioguanine nucleotides in the liver." Azathioprine is used to treat non-IBD autoimmune diseases (including dermatological and rheumatological autoimmune diseases).

	Court's Order of November 21, 2005.] The phrase "about 400 pmol per 8 x 10^{8}" means 400 +/- 15%, or 400 +/- 60 pmol per 8 x 10^{8} or 340-460 pmol per 8 x 10^{8}; thus a level of 450 pmol per 8 x 10^{8} is within about 400 pmol per 8 x 10^{8}. [*See* Court's Order of November 21, 2005.]
Accused Instrumentality: Inducing Mayo Clinic Rochester to measure 6-thioguanine and 6-methyl mercaptopurine levels in 5 of Dr. Sandborn's patients who had received azathioprine for immune-mediated gastrointestinal disorders, and providing levels, with interpretations of levels, to Dr. Sandborn or a person working for Dr. Sandborn (hereinafter, "Sandborn's Uses"). As part of the development and validation of Mayo's Test for Mayo, Mayo Clinic Rochester performed Mayo's Test on five patients' blood samples. [*See* Rule 30(b)(6) Dep. Trans. (May 25, 2005) at 112:7-113:5]. Because Mayo Clinic Rochester developed and validated Mayo's Test for Mayo, all work on Sandborn's Uses was induced by Mayo. These five patients were the patients of William Sandborn, a physician at Mayo Clinic Rochester. [*See id.* at 124:21-25]. Dr. Sandborn works with gastrointestinal disorders. [*See* http://mayoresearch.mayo.edu/mayo/research/staff/sandborn_wj.cfm.]. These five patients' blood samples had levels of 6-TGN measured by the Biochemical Genetics Laboratory at Mayo Clinic Rochester. [*See* MAYO002354-2567at MAYO002555, 2381, 2378, 2390, 2436, 2459]. Mayo Clinic Rochester compared the results of Mayo's Test on these five samples with results received from Prometheus. [*See id.*].	
U.S. Patent No. 6,355,623 All Claims Have a Priority Date of September 24, 1998	
Claim 1 – Literal infringement of all elements	
1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:	Each of the 5 patients in the Sandborn's Uses received azathioprine (from Dr. Sandborn or someone working for Dr. Sandborn) for treating

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and	an immune-mediated gastrointestinal disorder, including inflammatory bowel disease. The azathioprine was metabolized to 6-thioguanine after being administered to the patient; thus azathioprine provided 6-thioguanine to each of the 5 patients.
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,	Sandborn's Uses involved the determination of the level of 6-thioguanine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester measured the level of 6-thioguanine in each of the 5 patients.
wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and	For each of the 5 patients in the Sandborn Uses, a sample of blood was sent to Prometheus and the Biochemical Genetics Laboratory at Mayo Clinic Rochester. The Biochemical Genetics Laboratory at Mayo Clinic Rochester provided Dr. Sandborn, or someone working with Dr. Sandborn, the 6-TGN levels for each of the 5 patients. Further, Mayo and/or the Biochemical Genetics Laboratory at Mayo Clinic Rochester provided to Dr. Sandborn the 6-TGN results for each of these 5 patients as measured by Prometheus. The Prometheus test results state that levels of 6-TGN greater than 230 pmol/8x10^8 red blood cells is associated with a "Higher Likelihood of Response." Such information informed (and thus "indicated a

	need") the Biochemical Genetics Laboratory and Dr. Sandborn (or someone working for Dr. Sandborn) that the next dose of azathioprine given to the patient should be increased.
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	For each of the 5 patients in the Sandborn Uses, a sample of blood was sent to Prometheus and the Biochemical Genetics Laboratory at Mayo Clinic Rochester. The Biochemical Genetics Laboratory at Mayo Clinic Rochester provided Dr. Sandborn, or someone working with Dr. Sandborn, the 6-TGN levels for each of the 5 patients. Further, Mayo and/or the Biochemical Genetics Laboratory at Mayo Clinic Rochester provided to Dr. Sandborn the 6-TGN results for each of these 5 patients as measured by Prometheus. The Prometheus test results state that levels of 6-TGN greater than 400 pmol/8x10^8 red blood cells is associated with a "Higher Risk of Leucopenia." Such information informed (and thus "indicated a need") the Biochemical Genetics Laboratory and Dr. Sandborn (or someone working for Dr. Sandborn) that the next dose of azathioprine given to the patient should be decreased.
Claim 6 – Literal infringement of all elements	
6. The method of claim 5, wherein said level is determined using high pressure liquid	Sandborn's Uses used high performance liquid chromatography to determine the level of 6-

chromatography.	thioguanine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester used this technique to determine the level of 6-TGN and 6-MMP in the patient's blood sample. High performance liquid chromatography is a synonym for High Pressure Liquid Chromatography.
Claim 32 – Literal infringement of all elements	
32. The method of claim 1, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.	Each of the 5 patients in the Sandborn's Uses had been administered azathioprine by Dr. Sandborn or someone working for Dr. Sandborn.
Claim 7 – Literal infringement of all elements	
7. A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;	Each of the 5 patients in the Sandborn's Uses received azathioprine (from Dr. Sandborn or someone working for Dr. Sandborn) for treating an immune-mediated gastrointestinal disorder, including inflammatory bowel disease. The azathioprine was metabolized to 6-thioguanine after being administered to the patient; thus azathioprine provided 6-thioguanine to each of the 5 patients.
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and	Sandborn's Uses involved the determination of the level of 6-thioguanine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester measured the level of 6-thioguanine in each of the 5 patients.

(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,	Sandborn's Uses involved the determination of the level of 6-methylmercaptopurine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester measured the level of 6-methylmercaptopurine in each of the 5 patients.
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells or the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	For each of the 5 patients in the Sandborn Uses, a sample of blood was sent to Prometheus and the Biochemical Genetics Laboratory at Mayo Clinic Rochester. The Biochemical Genetics Laboratory at Mayo Clinic Rochester provided Dr. Sandborn, or someone working with Dr. Sandborn, the 6-TGN levels for each of the 5 patients. Further, Mayo and/or the Biochemical Genetics Laboratory at Mayo Clinic Rochester provided to Dr. Sandborn the 6-TGN results for each of these 5 patients as measured by Prometheus. The Prometheus test results state that levels of 6-TGN greater than 400 pmol/8x10^8 red blood cells is associated with a "Higher Risk of Leucopenia." Such information informed (and thus "indicated a need") the Biochemical Genetics Laboratory and Dr. Sandborn (or someone working for Dr. Sandborn) that the next dose of azathioprine given to the patient should be decreased.
Claim 14 – Literal infringement of all elements	

24	Accused Instrumentality: Inducing Mayo Clinic Rochester to measure 6-thioguanine and 6-methyl
25	mercaptopurine levels in Dr. el-Azhary's patients who had received azathioprine for immune-
26	mediated dermatological conditions, and providing levels, with interpretations of levels, to Dr. el-
27	Azhary or her associates (hereinafter, "el-Azhary's Uses").
28	

As part of the development, validation and training for Mayo's Test for Mayo, Mayo Clinic Rochester measured 6-TGN metabolite levels in hundreds of samples of blood from dermatological patients. Because Mayo Clinic Rochester developed, validated and trained for Mayo's Test for Mayo, all work on el-Azhary's Uses was induced by Mayo. These dermatological patients were patients of Dr. Rokea el-Azhary, a physician at Mayo Clinic Rochester. Dr. el-Azhary's patients had dermatologic autoimmune diseases. [*See* MAYO008250-8263]. These patients were treated with azathioprine, which provides 6-TGN to the patient. [*See id.* at MAYO008250]. The Biochemical Genetics Laboratory at Mayo Clinic Rochester determined the levels of 6-TGN in the patients' blood. [*See* MAYO002343-44; MAYO002334-2342; Rule 30(b)(6) Dep. Trans. (May 25, 2005) at 147:4-16, 159:15-25]. The reports of test results were transmitted to the doctor performing the study and the results advised the doctor that the "therapeutic range" was "235-400." [*See* MAYO002343-44 at MAYO002344; Rule 30(b)(6) Dep. Trans. (May 25, 2005) at 152:2-7, 152:11-15].	
U.S. Patent No. 6,355,623 All Claims Have a Priority Date of September 24, 1998	
Claim 22 – Literal infringement of all elements	
22. A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease, comprising: (a) administering a drug providing 6-thioguanine to a subject having said non-IBD autoimmune disease; and	Each of the patients in the el-Azhary's Uses were administered azathioprine (by Dr. el-Azhary or someone working with Dr. el-Azhary) for the treatment of an autoimmune dermatological condition such as bullous pemphigoid and pemphigus vulgaris (all of which are non-IBD autoimmune diseases). The azathioprine was metabolized to 6-thioguanine after being administered to the patient; thus azathioprine provided 6-thioguanine to each of the patients.
(b) determining the level of 6-thioguanine in	The Biochemical Genetics Laboratory at Mayo

said subject having said non-IBD autoimmune disease,	Clinic Rochester determined the level of 6-thioguanine in each of the patients in el-Azhary's Uses.
wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to said subject and	The Biochemical Genetics Laboratory at Mayo Clinic Rochester sent a report of test results to Dr. el-Azhary, or someone working for Dr. el-Azhary. The test results described the "therapeutic range" as "235-400." The Biochemical Genetics Laboratory at Mayo Clinic Rochester did not subsequently advise Dr. el-Azhary that the "therapeutic range" was not "235-400." Such information informed Dr. el-Azhary, or someone working for Dr. el-Azhary (and thus "indicated a need"), that the next dose of azathioprine given to the patient should be increased in order to be within the "therapeutic range." The phrase "about 230 pmol per 8 x 10^8" means 230 +/- 15%, or 230 +/- 34 pmol per 8 x 10^8; thus a level of 235 pmol per 8 x 10^8 is within about 230 pmol per 8 x 10^8. Azathioprine is a 6-mercaptopurine drug because azathioprine is converted to 6-mercaptopurine in the body of patients who have been administered azathioprine.
wherein the level of 6-thioguanine greater than	The Biochemical Genetics Laboratory at Mayo

about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to said subject.	Clinic Rochester sent a report of test results to Dr. el-Azhary, or someone working for Dr. el-Azhary. The test results described the "therapeutic range" as "235-400." The Biochemical Genetics Laboratory at Mayo Clinic Rochester did not subsequently advise Dr. el-Azhary that the "therapeutic range" was not "235-400." Such information informed Dr. el-Azhary, or someone working for Dr. el-Azhary (and thus "indicated a need"), that the next dose of azathioprine given to the patient should be decreased in order to be within the "therapeutic range." Azathioprine is a 6-mercaptopurine drug because azathioprine is converted to 6-mercaptopurine in the body of patients who have been administered azathioprine.

	Pressure Liquid Chromatography.
Claim 35 – Literal infringement of all elements	
35. The method of claim 22, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.	Each of the patients in el-Azhary's Uses had been administered azathioprine by Dr. el-Azhary or someone working with Dr. el-Azhary.

ATTACHMENT B

Prometheus' Disclosures Pursuant to Case Management Conference Order Items 2(a)-(c), (e) for defendant Mayo Clinic Rochester

Accused Instrumentality: The use of Test Code# 83306, entitled "Azathioprine Metabolites Profile, Blood," described in "Implementation Notice: New Test" dated June 9, 2004 from Mayo (hereinafter, "Mayo's Test") by any Mayo Clinic Rochester physician.	
U.S. Patent No. 6,355,623 **All Claims Have a Priority Date of September 24, 1998**	
Claim 1 – Literal infringement of all elements	
1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:	Mayo's Test, offered for sale on June 9, 2004, is for "[m]onitoring azathioprine therapy" in patients. Azathioprine "is converted to 6-thioguanine nucleotides in the liver." Mayo's Test was designed for and offered to physicians who treat patients with immune-mediated gastrointestinal disorders (including inflammatory bowel disease) using azathioprine. [*See* Implementation Notice.] Mayo Clinic Rochester's physicians provide azathioprine to treat patients with immune-mediated gastrointestinal disorders.
(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and	
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,	The Implementation Notice for Mayo's Test states that it provides physicians with the level of 6-TGN in a patient's blood using High Performance Liquid Chromatography. These patients have immune-mediated gastrointestinal disorders (including inflammatory bowel disease). [*See* Implementation Notice.] The

	Biochemical Genetics Laboratory at Mayo Clinic Rochester determines 6-TGN in a patient's blood for Mayo.
wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and	The Implementation Notice for Mayo's Test states that a 6-TGN level greater than 235 pmol/8X10(8) is the "therapeutic range" and that "[r]emission is associated with 6-TGN levels grater that [sic] 235 pmol/8X10(8) cells." Such information informs a physician that the next dose of azathioprine given to the patient should be increased (and thus "indicates a need to increase the amount of said drug subsequently administered to said subject"). [*See* Implementation Notice and Court's Order of November 21, 2005.] The phrase "about 230 pmol per 8 x 10^{8}" means 230 +/- 15%, or 230 +/- 34 pmol per 8 x 10^8; thus a level of 235 pmol per 8 x 10^8 is within about 230 pmol per 8 x 10^8. The Biochemical Genetics Laboratory at Mayo Clinic Rochester provides the Mayo Clinic Rochester physicians who order Mayo's Test the aforementioned information.
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	The Implementation Notice for Mayo's Test states that a 6-TGN level greater than "450 pmol/8X10(8)" is correlated with "Possible Myelosuppression," and that "[l]evels of 6-TGN

	greater that [sic] 450 pmol/8X10(8) cells have been associated with increased risk of myelosuppression, liver injury, pancreatitis, and allergic reactions." Such information informs a physician that the next dose of azathioprine given to the patient should be decreased (and thus "indicates a need to decrease the amount of said drug subsequently administered to said subject"). [*See* Implementation Notice and Court's Order of November 21, 2005.] The phrase "about 400 pmol per 8 x 10^8" means 400 +/- 15%, or 400 +/- 60 pmol per 8 x 10^8 or 340-460 pmol per 8 x 10^8; thus a level of 450 pmol per 8 x 10^8 is within about 400 pmol per 8 x 10^8. [*See* Court's Order of November 21, 2005.] The Biochemical Genetics Laboratory at Mayo Clinic Rochester provides the Mayo Clinic Rochester physicians who order Mayo's Test the aforementioned information.
Claim 6 – Literal infringement of all elements	
6. The method of claim 5, wherein said level is determined using high pressure liquid chromatography.	For those who order Mayo's Test, the Biochemical Genetics Laboratory at Mayo Clinic Rochester uses high pressure liquid chromatography to determine the level of 6-thioguanine in the patient.
Claim 32 – Literal infringement of all elements	
32. The method of claim 1, wherein said drug is	Mayo Clinic Rochester's physicians administer

selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.	azathioprine to patients with immune-mediated gastrointestinal disorders.
Claim 7 – Literal infringement of all elements	
7. A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;	Mayo's Test, offered for sale on June 9, 2004, is for "[m]onitoring azathioprine therapy" in patients. Azathioprine "is converted to 6-thioguanine nucleotides in the liver." Mayo's Test was designed for and offered to physicians who treat patients with immune-mediated gastrointestinal disorders (including inflammatory bowel disease) using azathioprine. [*See* Implementation Notice.] Mayo Clinic Rochester's physicians provide azathioprine to treat patients with immune-mediated gastrointestinal disorders.
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and	The Implementation Notice for Mayo's Test states that it provides physicians with the level of 6-TGN in a patient's blood using High Performance Liquid Chromatography. These patients have immune-mediated gastrointestinal disorders (including inflammatory bowel disease). [*See* Implementation Notice.] The Biochemical Genetics Laboratory at Mayo Clinic Rochester determines 6-TGN in a patient's blood for Mayo.
(c) determining the level of 6-methyl-	The Implementation Notice for Mayo's Test

mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,	states that it provides physicians with the level of 6-methylmercaptopurine in a patient's blood using High Performance Liquid Chromatography. These patients have immune-mediated gastrointestinal disorders (including inflammatory bowel disease). [*See* Implementation Notice.] The Biochemical Genetics Laboratory at Mayo Clinic Rochester determines 6-methylmercaptopurine in a patient's blood for Mayo.
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells or the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	The Implementation Notice for Mayo's Test states that a 6-TGN level greater than "450 pmol/8X10(8)" is correlated with "Possible Myelosuppression," and that "[l]evels of 6-TGN greater that [sic] 450 pmol/8X10(8) cells have been associated with increased risk of myelosuppression, liver injury, pancreatitis, and allergic reactions." Such information informs a physician that the next dose of azathioprine given to the patient should be decreased (and thus "indicates a need to decrease the amount of said drug subsequently administered to said subject"). [*See* Implementation Notice and Court's Order of November 21, 2005.] The phrase "about 400 pmol per 8 x 10^{8}" means 400 +/- 15%, or 400 +/- 60 pmol per 8 x 10^8 or 340-460 pmol per 8 x 10^8; thus a level of 450 pmol

	per 8 x 10^8 is within about 400 pmol per 8 x 10^8. [*See* Court's Order of November 21, 2005.] The Biochemical Genetics Laboratory at Mayo Clinic Rochester provides the Mayo Clinic Rochester physicians who order Mayo's Test the aforementioned information.
Claim 14 – Literal infringement of all elements	
14. The method of claim 13, wherein said level is determined using high pressure liquid chromatography.	For those who order Mayo's Test, the Biochemical Genetics Laboratory at Mayo Clinic Rochester uses high pressure liquid chromatography to determine the level of 6-thioguanine in the patient.
Claim 33 – Literal infringement of all elements	
33. The method of claim 7, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.	Mayo Clinic Rochester's physicians administer azathioprine to patients with immune-mediated gastrointestinal disorders.
Claim 22 – Literal infringement of all elements	
22. A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease, comprising: (a) administering a drug providing 6-thioguanine to a subject having said non-IBD autoimmune disease; and	Mayo's Test, offered for sale on June 9, 2004, is for "[m]onitoring azathioprine therapy" in patients. Azathioprine "is converted to 6-thioguanine nucleotides in the liver." Azathioprine is used by Mayo Clinic Rochester physicians to treat non-IBD autoimmune diseases (including dermatological and rheumatological autoimmune diseases). Mayo's Test is thus designed for physicians who treat

	the aforementioned information.
and wherein a level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells or a level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	The Implementation Notice for Mayo's Test states that a 6-TGN level greater than "450 pmol/8X10(8)" is correlated with "Possible Myelosuppression," and that "[l]evels of 6-TGN greater that [sic] 450 pmol/8X10(8) cells have been associated with increased risk of myelosuppression, liver injury, pancreatitis, and allergic reactions." Such information informs a physician that the next dose of azathioprine given to the patient should be decreased (and thus "indicates a need to decrease the amount of said drug subsequently administered to said subject"). [*See* Implementation Notice and Court's Order of November 21, 2005.] The phrase "about 400 pmol per 8 x 10^8" means 400 +/- 15%, or 400 +/- 60 pmol per 8 x 10^8 or 340-460 pmol per 8 x 10^8; thus a level of 450 pmol per 8 x 10^8 is within about 400 pmol per 8 x 10^8. [*See* Court's Order of November 21, 2005.] The Biochemical Genetics Laboratory at Mayo Clinic Rochester provides the Mayo Clinic Rochester physicians who order Mayo's Test the aforementioned information.
Accused Instrumentality: MCR's measurement of 6-thioguanine and 6-methyl mercaptopurine levels in 5 of Dr. Sandborn's patients who had received azathioprine for immune-mediated gastrointestinal disorders, and provision of levels, with interpretations of levels, to Dr. Sandborn or	

a person working for Dr. Sandborn (hereinafter, "Sandborn's Uses").

As part of the development of Mayo's Test for Mayo, Mayo Clinic Rochester performed Mayo's Test on five patients' blood samples. [*See* Rule 30(b)(6) Dep. Trans. (May 25, 2005) at 112:7-113:5]. These five patients were the patients of William Sandborn, a physician at Mayo Clinic Rochester. [*See id.* at 124:21-25]. Dr. Sandborn works with gastrointestinal disorders. [*See* http://mayoresearch.mayo.edu/mayo/research/staff/sandborn_wj.cfm.]. These five patients' blood samples had levels of 6-TGN measured by the Biochemical Genetics Laboratory at Mayo Clinic Rochester. [*See* MAYO002354-2567at MAYO002555, 2381, 2378, 2390, 2436, 2459]. Mayo Clinic Rochester compared the results of Mayo's Test on these five samples with results received from Prometheus. [*See id.*].

U.S. Patent No. 6,355,623
All Claims Have a Priority Date of September 24, 1998

Claim 1 – Literal infringement of all elements

1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and	Each of the 5 patients in the Sandborn's Uses received azathioprine (from Dr. Sandborn or someone working for Dr. Sandborn) for treating an immune-mediated gastrointestinal disorder. The azathioprine was metabolized to 6-thioguanine after being administered to the patient; thus azathioprine provided 6-thioguanine to each of the 5 patients.
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,	Sandborn's Uses involved the determination of the level of 6-thioguanine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester measured the level of 6-thioguanine in each of the 5 patients.
wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells	For each of the 5 patients in the Sandborn Uses, a sample of blood was sent to Prometheus and

indicates a need to increase the amount of said drug subsequently administered to said subject and	the Biochemical Genetics Laboratory at Mayo Clinic Rochester. The Biochemical Genetics Laboratory at Mayo Clinic Rochester provided Dr. Sandborn, or someone working with Dr. Sandborn, the 6-TGN levels for each of the 5 patients. Further, Mayo and/or the Biochemical Genetics Laboratory at Mayo Clinic Rochester provided to Dr. Sandborn the 6-TGN results for each of these 5 patients as measured by Prometheus. The Prometheus test results state that levels of 6-TGN greater than 230 pmol/8x10^8 red blood cells is associated with a "Higher Likelihood of Response." Such information informed (and thus "indicated a need") the Biochemical Genetics Laboratory and Dr. Sandborn (or someone working for Dr. Sandborn) that the next dose of azathioprine given to the patient should be increased.
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	For each of the 5 patients in the Sandborn Uses, a sample of blood was sent to Prometheus and the Biochemical Genetics Laboratory at Mayo Clinic Rochester. The Biochemical Genetics Laboratory at Mayo Clinic Rochester provided Dr. Sandborn, or someone working with Dr. Sandborn, the 6-TGN levels for each of the 5 patients. Further, Mayo and/or the Biochemical Genetics Laboratory at Mayo Clinic Rochester

	provided to Dr. Sandborn the 6-TGN results for each of these 5 patients as measured by Prometheus. The Prometheus test results state that levels of 6-TGN greater than 400 pmol/8x10^8 red blood cells is associated with a "Higher Risk of Leucopenia." Such information informed (and thus "indicated a need") the Biochemical Genetics Laboratory and Dr. Sandborn (or someone working for Dr. Sandborn) that the next dose of azathioprine given to the patient should be decreased.
Claim 6 – Literal infringement of all elements	
6. The method of claim 5, wherein said level is determined using high pressure liquid chromatography.	Sandborn's Uses used high performance liquid chromatography to determine the level of 6-thioguanine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester used this technique to determine the level of 6-TGN and 6-MMP in the patient's blood sample. High performance liquid chromatography is a synonym for High Pressure Liquid Chromatography.
Claim 32 – Literal infringement of all elements	
32. The method of claim 1, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine, and 6-methylmercaptopurine riboside.	Each of the 5 patients in Sandborn's Uses were administered azathioprine by Dr. Sandborn or someone working for Dr. Sandborn as part of his/her treatment for an immune-mediated gastrointestinal disorder.

Claim 7 – Literal infringement of all elements	
7. A method of reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder;	Each of the 5 patients in the Sandborn's Uses received azathioprine (from Dr. Sandborn or someone working for Dr. Sandborn) for treating an immune-mediated gastrointestinal disorder. The azathioprine was metabolized to 6-thioguanine after being administered to the patient; thus azathioprine provided 6-thioguanine to each of the 5 patients.
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder; and	Sandborn's Uses involved the determination of the level of 6-thioguanine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester measured the level of 6-thioguanine in each of the 5 patients.
(c) determining the level of 6-methyl-mercaptopurine in said subject having said immune-mediated gastrointestinal disorder,	Sandborn's Uses involved the determination of the level of 6- methyl-mercaptopurine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester measured the level of 6- methyl-mercaptopurine in each of the 5 patients.
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells or the level of 6-methyl-mercaptopurine greater than about 7000 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	For each of the 5 patients in the Sandborn Uses, a sample of blood was sent to Prometheus and the Biochemical Genetics Laboratory at Mayo Clinic Rochester. The Biochemical Genetics Laboratory at Mayo Clinic Rochester provided Dr. Sandborn, or someone working with Dr. Sandborn, the 6-TGN levels for each of the 5

	patients. Further, Mayo and/or the Biochemical Genetics Laboratory at Mayo Clinic Rochester provided to Dr. Sandborn the 6-TGN results for each of these 5 patients as measured by Prometheus. The Prometheus test results state that levels of 6-TGN greater than 400 pmol/8x10^{8} red blood cells is associated with a "Higher Risk of Leucopenia." Such information informed (and thus "indicated a need") the Biochemical Genetics Laboratory and Dr. Sandborn (or someone working for Dr. Sandborn) that the next dose of azathioprine given to the patient should be decreased.
Claim 14 – Literal infringement of all elements	
14. The method of claim 13, wherein said level is determined using high pressure liquid chromatography.	Sandborn's Uses used high performance liquid chromatography to determine the level of 6-thioguanine in the patient because the Biochemical Genetics Laboratory at Mayo Clinic Rochester used this technique to determine the level of 6-TGN and 6-MMP in the patient's blood sample. High performance liquid chromatography is a synonym for High Pressure Liquid Chromatography.
Claim 33 – Literal infringement of all elements	
33. The method of claim 7, wherein said drug is selected from the group consisting of 6-mercaptopurine, azathioprine, 6-thioguanine,	Each of the 5 patients in Sandborn's Uses were administered azathioprine by Dr. Sandborn or someone working for Dr. Sandborn as part of

Accused Instrumentality: MCR's measurement of 6-thioguanine and 6-methyl mercaptopurine levels in Dr. el-Azhary's patients who had received azathioprine for immune-mediated dermatological conditions, and provision of levels, with interpretations of levels, to Dr. el-Azhary or her associates (hereinafter, "el-Azhary's Uses"). As part of the development, validation and training for Mayo's Test for Mayo, Mayo Clinic Rochester measured 6-TGN metabolite levels in hundreds of samples of blood from dermatological patients. These dermatological patients were patients of Dr. Rokea el-Azhary, a physician at Mayo Clinic Rochester. Dr. el-Azhary's patients had dermatologic autoimmune diseases. [*See* MAYO008250-8263]. These patients were treated with azathioprine, which provides 6-TGN to the patient. [*See Id.* at MAYO008250]. The Biochemical Genetics Laboratory at Mayo Clinic Rochester determined the levels of 6-TGN in the patients' blood. [*See* MAYO002343-44; MAYO002334-2342; Rule 30(b)(6) Dep. Trans. (May 25, 2005) at 147:4-16, 159:15-25]. The reports of test results were transmitted to the doctor performing the study and the results advised the doctor that the "therapeutic range" was "235-400." [*See* MAYO002343-44 at MAYO002344; Rule 30(b)(6) Dep. Trans. (May 25, 2005) at 152:2-7, 152:11-15].
U.S. Patent No. 6,355,623 **All Claims Have a Priority Date of September 24, 1998**

Claim 22 – Literal infringement of all elements

22. A method of optimizing therapeutic efficacy of treatment of a non-IBD autoimmune disease,	Each of the patients in the el-Azhary's Uses were administered azathioprine (by Dr. el-

comprising: (a) administering a drug providing 6-thioguanine to a subject having said non-IBD autoimmune disease; and	Azhary or someone working with Dr. el-Azhary) for treating his/her autoimmune dermatological condition, such as bullous pemphigoid and pemphigus vulgaris (all of which are non-IBD autoimmune diseases). The azathioprine was metabolized to 6-thioguanine after being administered to the patient; thus azathioprine provided 6-thioguanine to each of the patients.
(b) determining the level of 6-thioguanine in said subject having said non-IBD autoimmune disease,	The Biochemical Genetics Laboratory at Mayo Clinic Rochester determined the level of 6-thioguanine in each of the patients in el-Azhary's Uses.
wherein the level of 6-thioguanine less than about 230 pmol per 8×10^8 red blood cells indicates a need to increase the amount of 6-mercaptopurine drug subsequently administered to said subject and	The Biochemical Genetics Laboratory at Mayo Clinic Rochester sent a report of test results to Dr. el-Azhary, or someone working for Dr. el-Azhary. The test results described the "therapeutic range" as "235-400." The Biochemical Genetics Laboratory at Mayo Clinic Rochester did not subsequently advise Dr. el-Azhary that the "therapeutic range" was not "235-400." Such information informed Dr. el-Azhary, or someone working for Dr. el-Azhary (and thus "indicated a need"), that the next dose of azathioprine given to the patient should be increased in order to be within the "therapeutic

	range." The phrase "about 230 pmol per 8 x 10^8" means 230 +/- 15%, or 230 +/- 34 pmol per 8 x 10^8; thus a level of 235 pmol per 8 x 10^8 is within about 230 pmol per 8 x 10^8. Azathioprine is a 6-mercaptopurine drug because azathioprine is converted to 6-mercaptopurine in the body of patients who have been administered azathioprine.
wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of 6-mercaptopurine drug subsequently administered to said subject.	The Biochemical Genetics Laboratory at Mayo Clinic Rochester sent a report of test results to Dr. el-Azhary, or someone working for Dr. el-Azhary. The test results described the "therapeutic range" as "235-400." The Biochemical Genetics Laboratory at Mayo Clinic Rochester did not subsequently advise Dr. el-Azhary that the "therapeutic range" was not "235-400." Such information informed Dr. el-Azhary, or someone working for Dr. el-Azhary (and thus "indicated a need"), that the next dose of azathioprine given to the patient should be decreased in order to be within the "therapeutic range." Azathioprine is a 6-mercaptopurine drug because azathioprine is converted to 6-mercaptopurine in the body of patients who

1		have been adminstered azathioprine.
2		

PETITIONER'S BRIEF

RECORD
AND

No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

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QUESTION PRESENTED

Prometheus's patents, which the district court invalidated but the Federal Circuit upheld, give Prometheus a sweeping monopoly on a biological correlation between drug administration and natural changes in blood chemistry. If these patents are sustained, health care providers, such as Mayo Clinic, cannot improve the numbers Prometheus has assigned to this correlation and provide more accurate drug monitoring services to patients at a lower cost, without permission from Prometheus.

The question presented is:

Whether 35 U.S.C. § 101 is satisfied by a patent claim that covers observed correlations between blood test results and patient health, so that the patent effectively preempts use of the naturally occurring correlations, simply because well-known methods used to administer prescription drugs and test blood may involve "transformations" of body chemistry.

RULES 24(b) AND 29.6 STATEMENT

All parties are identified in the caption of this brief. Petitioner Mayo Collaborative Services, a subsidiary of Mayo Clinic, is a for-profit Minnesota corporation that provides reference laboratory services under the name Mayo Medical Laboratories. Petitioner Mayo Clinic Rochester, a subsidiary of Mayo Clinic, is a charitable, nonprofit corporation located in Rochester, Minnesota. No publicly held company owns 10% or more of the stock of either petitioner.

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BRIEF FOR PETITIONERS

OPINIONS BELOW

The Federal Circuit's opinion following remand from this Court (Pet. App. 1a-23a) is reported at 628 F.3d 1347 (Fed. Cir. 2010). This Court's order granting certiorari, vacating, and remanding in light of *Bilski* v. *Kappos* (Pet. App. 24a) is reported at 130 S. Ct. 3218 (2010). The Federal Circuit's original opinion (Pet. App. 25a-49a) is reported at 581 F.3d 1336 (Fed. Cir. 2009). The district court's opinion holding Prometheus's patent claims invalid (Pet. App. 50a-83a) is reported at 2008 WL 878910 (S.D. Cal. Mar. 28, 2008).

JURISDICTION

The court of appeals entered its judgment on December 17, 2010, and this Court granted a timely petition for certiorari on June 20, 2011. The jurisdiction of this Court rests on 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101.

"The term 'process' means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material." 35 U.S.C. § 100(b).

INTRODUCTION

For more than a century, this Court has made clear that a patent claim fails under 35 U.S.C. § 101 if it preempts all practical use of an abstract idea, natural phenomenon, or mathematical formula. The Court has explained that these fundamental tools of discovery must be available to all for use in developing new and better inventions.

Petitioners ask this Court to reaffirm that basic principle in the context of medical patents covering natural phenomena. The Prometheus patents claim a monopoly over consideration of a naturally occurring correlation between metabolites of a drug and the toxicity or efficacy of that drug, without specifying any concrete use of this correlation. As a result, the patents preempt all practical use of the naturally occurring correlation and are invalid under Section 101.

Justice Breyer has observed that broad and open-ended patents of this kind prevent "doctors from using their best medical judgment," "force doctors to spend unnecessary time and energy to enter into license agreements," "divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations," and "raise the cost of health care while inhibiting its effective delivery." *Laboratory Corp. of Am. Holdings* v. *Metabolite Labs.*, 548 U.S. 124, 138 (2006) ("*LabCorp*") (Breyer, Stevens, Souter, JJ., dissenting from dismissal of petition for certiorari). All these adverse effects are evident in this case. This Court should reverse the Federal Circuit's decision and invalidate Prometheus's patents under Section 101.

STATEMENT

A. Blood Testing For Metabolites.

All doctors know that a drug should be administered to a patient at a dose that is above an ineffective level but below a harmful level. Effective dosage ranges vary for each patient based on how a patient metabolizes the drug and on factors such as the patient's weight and medical condition.

Physicians often deal with these individual variations by analyzing blood samples for levels of "metabolites"—chemicals produced in the blood when a patient metabolizes a drug. The correlation between metabolites and patient condition is more consistent across a population than is the correlation between dosage levels and patient condition, so particular metabolite levels correlate generally with patient health. This is much like blood alcohol testing, where a certain blood alcohol level is a better indication of a person's condition, across a population, than the number of drinks the individual may have consumed.

Judgment plays a pivotal role in selecting the right correlation, as seen, by analogy, in the fact that many states initially set their acceptable blood alcohol level at 0.10, but adjusted it to 0.08 after further research. Case-by-case judgment also is needed because patient-to-patient variability cannot be removed entirely even by observing metabolite levels. The ability to question current wisdom, to develop better numbers, and to take into account relevant factors for each patient is critical to patient health and to our healthcare system. The *Wall Street Journal* recently reported that initial medical research is increasingly found to be wrong, and it

costs large amounts of money and many lives before such errors are corrected. Gautam Naik, *Mistakes in Scientific Studies Surge*, WALL ST. J., Aug. 10, 2011, available at http://tinyurl.com/43mf2ot. In making determinations about what metabolite numbers mean for patient health, the freedom to question old information and to improve on it is necessary to save lives.

B. The Patents At Issue.

The patents in this lawsuit involve blood testing after administration of a drug known as azathioprine, or thiopurine.[1] Thiopurine drugs have been administered for decades, and, as the patents admit, the appropriate levels of thiopurine metabolites in patients have been measured, studied, and discussed for many years. For example, English physicians studied them in the 1980s, and published articles about them relating to autoimmune diseases. See C.A. App. A12698-12701, A12705-12712, A12722-12727.

The inventors of the patents at issue here studied the correlations between thiopurine metabolite levels and the conditions of patients suffering

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[1] Azathioprine is the most commonly used thiopurine drug. It was sold under the brand name "Imuran" for years, and now is available in various generic forms. See FEDERAL DRUG ADMINISTRATION, ORANGE BOOK: APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS, available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Azathioprine "upon administration to a patient converts to 6-MP," which then "is broken down by the body into various 6-MP metabolites," including 6-TG (6-thioguanine) and 6-MMP (6-methyl-mercaptopurine). 6-TGN, referred to in many record documents, is a derivative of 6-TG. It is those metabolites that are covered by Prometheus's patents. Pet. App. 3a.

from gastrointestinal autoimmune diseases. They developed a database of pediatric patients with inflammatory bowel disease who had received thiopurine treatment. They used "methods well known in the art" to measure the metabolite levels in these patients. 2JA 11, at 9:13-14. Using these techniques, the inventors observed that patients seemed to get better when thiopurine's 6-TG (6-thioguanine) metabolite exceeded 230 picomoles per 800 million red blood cells and got worse when it exceeded 400 picomoles. The inventors also observed that patients got worse when thiopurine's 6-MMP (6-methyl-mercaptopurine) metabolite exceeded 7000 picomoles. They did not, however, "invent" these correlations between patient condition and metabolite levels, but merely recognized them as existing in the patient population that they studied. 1JA 15, 32.

The inventors worked at a teaching hospital in Montreal. There is no evidence that they ever considered patenting these natural correlations on their own. For example, well before the patents at issue were filed, the inventors freely disclosed in a paper in an academic journal the general association between thiopurine metabolites and the efficacy or toxicity of thiopurine therapy. Carmelo Cuffari *et al.*, *6-Mercaptopurine Metabolism in Crohn's Disease: Correlation with Efficacy and Toxicity*, 39 GUT 401 (1996). The patent acknowledges this prior work. See 2JA 10, at 8:37-46.

The inventors' publication apparently caught the eye of Prometheus. In 1998, Prometheus licensed the research from the inventors and their employer hospital, as recited in the complaint. C.A. App. A12597 ¶ 10. Apart from consulting fees, the inventors were

to be compensated only if Prometheus successfully commercialized their research. Within a few weeks of the execution of this license, Prometheus filed "provisional" patent applications on the inventors' research at the United States Patent and Trademark Office ("PTO"), from which the two patents at issue ultimately derived.[2]

Reflecting the academic background of the inventors, the Prometheus patents do not recite any real-world uses of the natural correlations between metabolite levels and patient health. Instead, they broadly encompass the mental recognition of the correlations by claiming (a) administering some undefined level of thiopurine to a person, and (b) considering whether that test dose is too small, within a therapeutic range, or too large based on observed metabolite levels, as exemplified by claim 1 of the '623 patent:

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of

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[2] The patents are U.S. Patents 6,355,623 ("the '623 patent") and 6,680,302 ("the '302 patent"), reproduced at 2JA 1-35.

> said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

2JA 16, at 20:9-25; see Pet. App. 3a-5a (describing the patent claims). Other claims, such as claim 46 of the '623 patent, do not even require the "administering" step, reciting only the step of "determining" metabolite levels. 2JA 18, at 23:41-24:17; Pet. App. 5a. Despite preamble language stating that these steps "optimiz[e] therapeutic efficacy," none of the claims describes any patient treatment, any change in dosage, or any other real-world use of the physician-recognized natural correlations. They thus cover, and preempt, any and all uses of the correlations.

Based on these patents, Prometheus brought to market a blood test for thiopurine metabolites under the trade name Pro-Predict. Hospitals and laboratories send patient blood samples to Prometheus for analysis of metabolite levels. Prometheus provides the test results along with a form that contains information about the 6-TG metabolite correlation recited in its patents.[3] An example of a Prometheus test result form appears at 2JA 36.

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[3] Prometheus's form did not set forth any information regarding its patented "7000" 6-MMP correlation. See 2JA 36; Pet. App. 3a, 52a. In a vivid demonstration of why patenting naturally observed relationships should not be allowed, it turned out that Prometheus's "7000" 6-MMP correlation was unreliable when extended to a larger population than had been covered by the

C. Mayo Clinic's Improvement Of The Prometheus Blood Test.

Mayo Clinic is one of the world's leading medical institutions in both patient care and research. A not-for-profit organization, Mayo's mission is to provide the best possible care to its patients through integrated clinical practice, education, and research.

Mayo Medical Laboratories ("Mayo Labs") is a global reference laboratory operating within Mayo Clinic's Department of Laboratory Medicine and Pathology. Mayo Labs provides clinical laboratory services to Mayo patients, as well as to other hospitals and clinics. While Mayo Labs is a for-profit organization, any profits it earns go directly to support Mayo's patient care, education, and research activities.

Mayo has long been a leader in the research of gastrointestinal disorders. And its physicians and researchers have published extensively in the area of thiopurine metabolites, including in papers cited in Prometheus's patents. 2JA 1-3, 19-21; see William J. Sandborn *et al.*, *Lack of Effect of Intravenous Administration on Time to Respond to Azathioprine for Steroid-Treated Crohn's Disease*, 117 GASTROENTEROLOGY 527 (1999). Mayo's gastroenterology practice is the largest in the United States. See http://www.mayoclinic.org/gi-rst. In any given year,

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inventors' original study. Accordingly, a "5700" 6-MMP correlation is widely used today. Indeed, even the "400" correlation for 6-TG has since been replaced by a "450" correlation, which itself is not a rigid cutoff. See 2JA 38-40.

Mayo physicians see over 30,000 gastroenterology patients. *Ibid.*[4]

For several years, Mayo Labs used Prometheus's Pro-Predict test, sending patient samples for testing to Prometheus. The results were accompanied by reports that included a description of Prometheus's patented 230-to-400 range. 2JA 36-37.

In 2003, Mayo Labs decided that it could improve upon the Pro-Predict test. In addition to developing better assays to measure metabolite levels, Mayo considered its own experience with thiopurine treatment and studied relevant literature to develop more detailed information to provide along with its test results. 2JA 38-39. See 1JA 10 (the improved, lower-priced Mayo test was designed to serve both "business" and "clinical" goals, the latter being "more important"); 1JA 8 (Mayo also aimed to provide faster service).

In June 2004, Mayo announced it would offer its own thiopurine metabolite test to compete with the Pro-Predict test. Like Prometheus, Mayo proposed to provide information with its test results. But unlike Prometheus, Mayo was not constrained by the need to conform to any patented invention, and provided more useful information with its test results. This information was to include the following (see 2 JA 38-39):

- A blood reading greater than 235 picomoles of 6-TGN is a "target therapeutic range," and a reading greater than 250

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[4] U.S. News & World Report recently ranked Mayo as the #1 hospital in the country for gastroenterology. See http://health.usnews.com/best-hospitals/rankings.

picomoles of 6-TGN is associated with remission in adult patients; and

- A blood reading greater than 450 picomoles of 6-TGN indicates possible adverse health effects, but in some instances levels over 700 are associated with remission without significant toxicity, while a "clearly defined toxic level" has not been established; and
- A blood reading greater than 5700 picomoles of 6-MMP is possibly toxic to the liver. See p. 7, n.3, *supra*.

An example of the information Mayo proposed to provide with its test is provided at 2JA 38-39. For further background on the information reported on its form, Mayo cited scholarship from six different scientific journals, dating from 1989 to 2003. *Ibid.* Physicians ordering the test would have access to Mayo doctors if they had questions about test results. See 2JA 40; http://www.mayomedicallaboratories.com/customer-service/index.html.

Mayo proposed to offer its test at a substantially lower price than Prometheus's test. In 2004, the average selling price of Prometheus's test was $262. Mayo proposed to price its test 25 percent less, at $193. 1JA 28. As Prometheus's expert acknowledged, Prometheus's monopoly had enabled it to exact a "price premium." *Ibid.*

D. Prometheus's Lawsuit Against Mayo Clinic.

Despite the "different levels" of metabolites used in Mayo's test (Pet. App. 6a, 52a) and the different information provided, Prometheus sued Mayo Medi-

cal Laboratories days after its announcement of the test. As a result of this litigation, Mayo never launched its test and has withheld it from the market for more than seven years.

This lawsuit seeking to block Mayo's test showed the sweeping breadth of the Prometheus patents. In particular, while Mayo sought to limit the claims to require a real-world use of the correlation, such as a physician's raising or lowering a dosage, Prometheus successfully argued to the district court that the patents required no concrete implementation of the mental recognition. Pet. App. 107a-110a.

The breadth of Prometheus's claims was further revealed when Prometheus attacked different research in a different field than that studied by the physicians who developed Prometheus's ranges. After obtaining a broad claim construction from the district court, Prometheus filed an amended complaint accusing Mayo of infringement based on a study of dermatology patients conducted by Mayo physician and researcher Dr. Rokea el-Azhary. See Pet. App. 77a n.10. Prometheus asserted that Dr. el-Azhary's study infringed the patents even though Dr. el-Azhary was entirely unconcerned with metabolite ranges for gastrointestinal disorders; her patients suffered from disfiguring autoimmune diseases of the skin. After prescribing thiopurine to her patients for treatment of these disorders, she collected data on their metabolite levels to see if she could establish a therapeutic range for dermatological disorders. 1JA 17-18. While she had heard of prior research in the gastrointestinal area, she testified that Prometheus's gastrointestinal-related metabolite levels were "irrelevant to [her] study" because "there is no reason to extrapolate to dermatology." 1JA 19.

But because a Mayo-generated lab report that Dr. el-Azhary received mentioned the ranges in the patents, Prometheus accused Mayo of infringement through her work:

> The Biochemical Genetics Laboratory at Mayo Clinic Rochester sent a report of test results to Dr. el-Azhary, or someone working for Dr. el-Azhary. The test results described the "therapeutic range" as "235-400." The Biochemical Genetics Laboratory at Mayo Clinic Rochester did not subsequently advise Dr. el-Azhary that the "therapeutic range" was not "235-400."
>
> Such information informed Dr. el-Azhary, or someone working for Dr. el-Azhary (and thus "indicated a need"), that the next dose of azathioprine given to the patient should be increased in order to be within the "therapeutic range."

2JA 55, 71-72.

Prometheus demanded and received discovery of all Dr. el-Azhary's patients' confidential records. Prometheus also required Dr. el-Azhary to answer hours of questions in deposition about these patients and her treatment of them. 1JA 19. Prometheus even asserted infringement against Dr. el-Azhary's work when she subsequently received reports that did not list the patented "therapeutic range"—because the ranges were ***still in her memory***. 1JA 20-22, 36-42. Once she had seen the patented range one time, there was nothing Dr. el-Azhary could do, Prometheus maintained, to avoid infringement. Its expert testified that Dr. el-Azhary's receipt of a test report would lead to infringement "[w]hether she crumples

it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with." 1JA 42.

According to Prometheus, Dr. el-Azhary must stop her dermatological research until she purges her memory of the correlations—regardless of how she ultimately may use any test results—because Prometheus's claims preempt all possible uses of the natural correlations. Indeed, anyone who sees Prometheus's numbers and a patient test report of metabolite levels is a potential infringer—even someone who reads about those ranges in this brief.

Dr. el-Azhary ultimately completed her study and reported that, for dermatology patients, a therapeutic range of metabolites is 150 to 300 picomoles—substantially different from the range postulated by Prometheus based on gastroenterology data. But because of Prometheus's allegations and this lawsuit, Mayo was forced to hold up publication of Dr. el-Azhary's study until the district court ruled for Mayo in 2008, lest it risk claims by Prometheus that her study induced other dermatologists to infringe the patents. As a result, the field of dermatology and its patients lacked access to that information for several years. See Rokea A. el-Azhary, *et al.*, *Thioguanine Nucleotides and Thiopurine Methyl-transferase in Immunobullous Diseases: Optimal Levels as Adjunctive Tools for Azathioprine Monitoring*, 145 ARCH. DERMATOL. 644 (June 2009).

E. The District Court's Decision.

Mayo moved for summary judgment, asserting that the Prometheus claims were not patent-eligible under 35 U.S.C. § 101. See Pet. App. 52a-54a. The district court granted the motion, finding that

Prometheus's claims recite correlations between thiopurine drug metabolite levels and therapeutic efficacy or toxicity that are natural phenomena. Pet. App. 63a-71a. As Prometheus's expert admitted, "the key therapeutic aspect of such thiopurine drugs is that they are converted naturally by enzymes within the patient's body to form an agent that is therapeutically active." Pet. App. 65a. Accordingly, the district court concluded (Pet. App. 66a) that Prometheus

> did not "create" the correlation between thiopurine drug metabolite levels and therapeutic efficacy and toxicity. Instead, the correlation results from a natural body process, which as the inventors concede, was pre-existing in the patient population, and it exists in the patient population today.

The court also explained that the steps of the claim reciting "administering" a drug and "determining" metabolite levels were "merely data-gathering steps" that were necessary precursors for reviewing the claimed correlation. Pet. App. 63a. All "the inventors claim to have discovered is that particular concentrations of [thiopurine metabolites] correlate with therapeutic efficacy and toxicity in patients taking AZA drugs." *Ibid.*

The district court quoted approvingly from the *LabCorp* opinion of Justices Breyer, Stevens, and Souter, which explained that the similar claim there failed "the requirement that it not amount to a simple natural correlation, *i.e.*, a 'natural phenomenon'" (citing this Court's precedents):

> At most, respondents have simply described the natural law at issue in the

> abstract patent language of a "process." But they cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge. One might, of course, reduce the "process" to a series of steps, e.g., Step 1: gather data; Step 2: read a number; Step 3: compare the number with the norm; Step 4: act accordingly. The question is what those steps embody. And here, aside from the unpatented test, they embody only the correlation between homocysteine and vitamin deficiency that the researchers uncovered. In my view, that correlation is an unpatentable "natural phenomenon," and I can find nothing in [the claim] that adds anything more of significance.

LabCorp, 548 U.S. at 137-138 (citation omitted), quoted at Pet. App. 67a-68a.

In light of its review of Prometheus's broad claims and of this Court's preemption precedents, the district court concluded that these claims improperly preempt a natural phenomenon. Applying this Court's preemption standard in *Gottshalk* v. *Benson*, 409 U.S. 63 (1972), and *Parker* v. *Flook*, 437 U.S. 584 (1978), the court refused to apply a mechanical "transformation" test. Pet. App. 73a-74a. It explained that Prometheus's claims preempt all uses of the physician-recognized natural correlations, because every activity recited in the claims, other than recognition of the correlations themselves, was simply data gathering necessary to observe the natural correlation (Pet. App. 75a-78a):

> what the inventors claim to have discovered is that particular concentrations of 6-TG and

6-MMP correlate with therapeutic efficacy and/or toxicity in patients taking AZA drugs. Because the claims cover the correlations themselves, it follows that the claims "wholly pre-empt" the correlations.

F. The Federal Circuit's Decisions.

The Federal Circuit reversed. It applied its own "machine-or-transformation" test as a "definitive" standard, and in a footnote glossed over the analysis in Justice Breyer's *LabCorp* opinion. Pet. App. 33a-43a & n.3. Prometheus had invited that ruling by arguing that "a freestanding preemption inquiry is inappropriate" because the "machine or transformation test is the singular test for a process claim under § 101." Prometheus Reply Br. at 21 n.3 (Fed. Cir. Apr. 24, 2009).

Mayo sought review by this Court. While Mayo's petition for certiorari was pending, this Court decided *Bilski* v. *Kappos*, 130 S. Ct. 3218 (2010). *Bilski* included three opinions, which all agreed on certain key points: (1) they disapproved of the Federal Circuit's rote reliance on "machine or transformation" as a standard, demanding a more nuanced inquiry; (2) they affirmed that natural phenomena and abstract ideas lie outside Section 101, so that claims that have the practical effect of preempting all practical uses of a natural phenomenon are invalid; and (3) they reaffirmed the decisions in *Benson*, *Flook*, and *Diamond* v. *Diehr*, 450 U.S. 175 (1981), and pointedly declined to endorse any prior Federal Circuit approach. Moreover, the opinions by Justice Stevens (joined by Justices Ginsburg, Breyer, and Sotomayer) and Justice Breyer (joined in relevant part by Justice Scalia) each referenced *LabCorp* approvingly. And

the majority opinion emphasized the need to set the Section 101 bar high enough to avoid flooding courts "with claims that would put a chill on creative endeavor and dynamic change." 130 S. Ct. at 3229. After deciding *Bilski*, this Court granted certiorari, vacated, and remanded in the present case. Pet. App. 24a.

On remand, Mayo reiterated its preemption argument. Mayo Supp. Br. to Fed. Cir. on Remand, at 1-2. Prometheus argued that its claims involve transformations and machines, apply natural laws in a particular context, and do not preempt a general concept. Prometheus Supp. Br. to Fed. Cir. on Remand, at 1-3. Prometheus also argued that any claim that recites a machine or transformation necessarily passes the preemption standard. *Id.* at 2. Without hearing oral argument, the Federal Circuit affirmed its prior decision.

The Federal Circuit concluded that *Bilski* "did not undermine" its prior analysis—which had equated this Court's preemption standard with the Federal Circuit's "machine-or-transformation" test. Pet. App. 14a. Consistent with that view, the Federal Circuit again held that transformations of matter occur when a patient's body metabolizes a drug and when blood is tested for metabolites, and that these "transformations" made the claims patentable. Pet. App. 15a-21a. As for preemption, the Federal Circuit reasoned that "the claims do not preempt all uses of the natural correlations; they utilize them in a series of specific steps" (Pet. App. 15a)—failing to recognize that the steps recited in the claims that lead up to a physician's review of the correlations are *not* uses of the correlations, and failing to recognize that the claims cover and preempt anything that a physician

might do with the correlations. As it did before, the Federal Circuit dismissed *LabCorp* summarily, stating that it "decline[d] to discuss a dissent"—even though Justice Breyer's opinion was the only word by any Justice on the merits of this critical issue. Pet. App. 16a n.2.

SUMMARY OF ARGUMENT

A. Prometheus's patents purport to monopolize the field of blood testing for thiopurine metabolites, covering *anything* a physician might do with knowledge of the natural correlation between metabolite levels and health across autoimmune diseases of any description. This Court's precedents establish that such claims do not satisfy Section 101. A patent may not preempt "laws of nature, physical phenomena, and abstract ideas," which are "free to all men and reserved exclusively to none." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980). That principle bars not only a patent claim aimed directly at a natural phenomenon, but also one whose "practical effect would be a patent on the [phenomenon] itself." *Gottschalk* v. *Benson*, 409 U.S. 63, 71-72 (1972). And it bars patents that preempt a significant field of activity, even if some other uses are left in the public domain. See *Parker* v. *Flook*, 437 U.S. 584, 589-590 (1978). This Court consistently has applied that understanding, most recently in *Bilski*, where each member of this Court agreed that a patent may not confer a monopoly over an abstract idea in a broad field of use.

Under this settled principle, Prometheus's claims are invalid. Prometheus's patents recite a natural phenomenon—the biological correlation between metabolite levels and health—without describing what is to be done with that phenomenon beyond

considering whether a dosage adjustment may be necessary. Because Prometheus's claims culminate with this open-ended "mental step" (Pet. App. 21a), their "practical effect" is to "wholly pre-empt" use of the natural correlation with regard to any auto-immune disease. *Benson*, 409 U.S. at 71-72. This point is not debatable. Prometheus acknowledges that, if its patents are valid, physicians may not *consider* thiopurine metabolite correlations without a license, and they infringe the patents by determining that Prometheus's metabolite ranges are medically *inappropriate*.

B. Prometheus cannot defend its patents by embedding a natural correlation in a "process" that includes "token" and "conventional" data-gathering steps—administering a drug and testing blood for metabolites of the drug—that are "well known" and "long prevalent" in medical practice. *Flook*, 437 U.S. at 594; *Diamond* v. *Diehr*, 450 U.S. 175, 193 n.14 (1981); *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3231 (2010). These steps do nothing to narrow the scope of preemption of the biological phenomenon; any physician seeking to improve Prometheus's criteria would inevitably go through the same preliminary steps. As Justice Breyer explained in *LabCorp*, 548 U.S. at 137-138, any conduct can be described as a "process" with "a series of steps," but the key legal question is "what those steps embody." Here, they embody "a simple natural correlation" combined with well-known steps that do nothing to prevent the claims from wholly preempting physicians' practical use of that correlation. *Id.* at 136-137.

The Prometheus patents are not saved by application of the "machine-or-transformation" test invoked by the Federal Circuit. *Bilski* held that a

"transformation" is simply one "clue" to patent eligibility and does not override the principle that "laws of nature" must be free for all to use. 130 S. Ct. at 3225-3226. Here, the "transformations" held dispositive by the Federal Circuit—changes in the human body resulting from administration of drugs and changes in the blood when tested for metabolites —are incidental to data-gathering, have no limiting effect on the claimed monopoly, and lack any connection to the goal of the patent system to promote innovation. Because it does not require a transformation that narrows the field of preemption, the Federal Circuit's test is mechanical and easily manipulated, leaving courts and patent examiners prone to arbitrary line drawing.

C. The legal principle that a patent may not preempt laws of nature was well established before Congress enacted Section 101 in its current form in 1952. Congress never would have intended to allow sweeping patent claims like Prometheus's that chill research and speech and prevent institutions like Mayo Clinic from identifying better metabolite ranges or marketing more accurate and inexpensive tests. It is unthinkable that Congress intended the patent laws to embargo independent research and thought about a natural correlation based on Prometheus's suggestion of numbers that it deems relevant, but which others may reasonably reject.

D. The impact of a proposed patent on innovation and competition has an important bearing on the patent's validity: "The underlying policy of the patent system [is] that 'the things which are worth to the public the embarrassment of an exclusive patent'" must "'outweigh the restrictive effect of the limited patent monopoly.'" *Bilski*, 130 S.

Ct. at 3258 (Breyer, J., concurring in the judgment). Here, the Prometheus patents are far more likely to retard than to advance innovation, and thus to frustrate the broader goals of patent law.

Patent protection assuredly is unnecessary to encourage or fund basic research of the sort reflected in the Prometheus patents, which is now routinely undertaken by scientists and researchers without regard to filing patents. But patents like those obtained by Prometheus are certain to *inhibit* innovation and the improvement of patient care. Such patents on basic scientific principles deter the research that drives innovation. This problem is particularly acute in the medical field, where ready access to basic facts (such as the relationship between levels of metabolites and a drug's efficacy) is essential to research; where giving a patentee monopoly control over essential medical observations will adversely affect the quality of patient care, increasing costs and reducing the availability of medical services; and where physicians have an ethical obligation to spread knowledge and improve diagnostic criteria for the benefit of all. For these reasons, Prometheus's attempt to monopolize basic biological relationships is insupportable.

ARGUMENT

Thiopurine drugs, discovered over thirty years ago, are powerful medicine. Too much can be fatal. Too little can result in unsuccessful therapy. For decades, doctors have drawn blood after administering these drugs, tested for metabolite levels, and adjusted dosage in light of their best medical judgment.

The Prometheus patents seek to monopolize these metabolite numbers. They advise physicians to think about the need for a dosage adjustment when metabolites reach certain levels, but do not offer any specific change in therapy. Thinking about metabolite levels is exactly what doctors have long done, without any advice from Prometheus.

When Mayo Clinic examined its own patient records, it concluded that different numbers would better serve patient health and avoid injury. It also tried to offer a better test—with quicker blood testing, advice from its own expert staff, and specific reference to adverse side effects of thiopurine drugs. Mayo wanted to offer its service to doctors nationwide at a cost considerably less than Prometheus charged, offering savings to millions of people who take thiopurine drugs and require multiple blood tests while being treated over months or years for serious illness.

Mayo never had a chance to offer this improved test because Prometheus sued to block it. According to Prometheus, its patents preempt the entire field of blood testing for thiopurine metabolites for patients with any autoimmune disease, so that others may not improve on or disagree with its medical advice. The Federal Circuit agreed with Prometheus that this perverse result is required by federal patent law. Nothing could be further from Congress's intention, this Court's precedents, or ordinary common sense. This Court should put an end to the embargo that Prometheus has imposed on medical research and scholarly criticism of its medical advice. Doctors and patients should have the right to choose between the medical advice offered by Mayo Clinic and Prometheus, or whoever else wishes to weigh in.

I. PROMETHEUS'S CLAIMS DO NOT SATISFY SECTION 101 OF THE PATENT ACT.

A. Prometheus's Claims Monopolize All Uses Of A Natural Biological Relationship.

Prometheus's claims have broad preclusive reach over a natural biological phenomenon. Each claim consists either of the three steps of administering a thiopurine drug, determining metabolite levels produced by the body in natural reaction to that drug, and then considering a metabolite range that may "indicat[e] a need" to change dosage (*e.g.*, Claim 1, Pet. App. 4a), or the last two steps only. Claim 46, Pet. App. 5a. Prometheus successfully argued in the district court that the final step does not "requir[e] doctors to adjust dosage if the metabolite level reaches the specified level," but is satisfied when a physician or researcher is "warned" or "notified" that a dosage adjustment *may* be indicated. Pet. App. 108a-109a; see also Pet. App. 23a (Federal Circuit observed that the patent's result is "useful information for possible dosage adjustments").

The correlation between metabolite levels and patient health is dictated by natural enzymatic activity inside the human body. Prometheus's expert admitted that thiopurine drugs are "converted naturally by enzymes within the patient's body" into metabolites, as the district court found. Pet. App. 65a. And, confirming that the correlations are natural phenomena, the developers of the metabolite ranges admitted that they did not "invent" them, but "merely observed these natural correlations by studying a 'database of patien[t] information.'" *Ibid.*; see 1JA 15-16, 32. The Federal Circuit did not

disturb the district court findings to that effect, and agreed that the correlations are "naturally occurring." Pet. App. 15a.

Prometheus concedes, as it must, that it seeks to patent "a truth" about "the physical world," but asserts that its claims are nevertheless valid because they recite preliminary "process steps that require concrete human actions." Br. in Opp. 21-22. The "administering" and "determining" steps of Prometheus's claims are not, however, its inventions. The drugs involved and the method of blood testing for metabolites are well known and have been used by physicians and researchers for decades. And those preliminary steps—which the district court found are "merely necessary data-gathering steps for any use of the correlations" (Pet. App. 62a)—do nothing to confine the scope of Prometheus's claims. They impose no limit because the final mental step—the only one to which Prometheus made any contribution—preempts all practical uses of naturally occurring correlations between these drugs and metabolite levels across all types of autoimmune disease.[5]

Prometheus has confirmed the sweeping preclusive scope of its patents by suing to prevent Mayo from marketing a test it developed to achieve more

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[5] Prometheus's claims do not recite the administration of any amount of any drug to be given to any patient. Patent drafters know how to recite administration of "a therapeutically effective amount" of a drug for method of treatment claims. See, *e.g.*, *Geneva Pharms., Inc.* v. *GlaxoSmithKline PLC*, 349 F.3d 1373, 1383-1384 (Fed. Cir. 2003) ("effective amount" is "a common and generally acceptable term" in claims covering pharmaceutical treatment methods); *Rapoport* v. *Dement*, 254 F.3d 1053, 1056 (Fed. Cir. 2001). Prometheus was careful not to do so here.

accurate results and improved patient care at a lower cost. Pet. App. 85a & n.2; 1JA 28. Prometheus insists that Mayo cannot develop a test with *different* criteria relating to *any* autoimmune disease unless it invents (needlessly) an entirely new way of examining the body for metabolites. Br. in Opp. 25, 27. And it maintains that a physician who knows of Prometheus's correlations cannot even decide *not* to use them without paying Prometheus. *Id.* at 24. Indeed, Prometheus's expert testified that a physician who receives test results referring to Prometheus's metabolite ranges infringes regardless whether she "crumples it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with." 1JA 40-42.

Prometheus thus asserts the power to prevent doctors and researchers—who considered metabolite levels on their own years before these patent claims were filed (see *supra*, p. 4)—from exercising independent medical judgment based on ordinary blood evaluations. That this is no exaggeration is shown by Prometheus's attack on Mayo researcher Dr. el-Azhary. Although Prometheus says that it "does not sue doctors" (Br. in Opp. 24), it sued her employer, deposed her for hours, examined her confidential patient records, and asserted that her study infringed Prometheus's patents because she administered drugs to dermatology patients with autoimmune diseases, tested their blood for metabolites, and investigated the optimal therapeutic range for dermatology patients. *Supra*, pp. 11-13. Dr. el-Azhary ultimately concluded—in a paper she dared not publish until the district court invalidated Prometheus's patents—that far different metabolite levels were necessary for dermatology patients. *Supra*, p. 13.

Similarly, a physician who seeks to investigate whether the appropriate metabolite ranges for patients with gastrointestinal disorders might vary with patient age, gender, presence of other diseases, or other relevant factors, could not do so without a license from Prometheus. It is clear, therefore, that Prometheus's claims monopolize the whole field, covering *anything* that a physician might do with her knowledge of the natural correlation between metabolite levels and health—even reject Prometheus's levels as detrimental to patient care.

B. This Court's Precedents Forbid Prometheus's Preemption Of A Natural Phenomenon.

This Court's precedents establish that claims like Prometheus's, which preempt all practical uses of a natural phenomenon across a broad field, do not satisfy Section 101.

1. Although Section 101 is expansive, "this is not to suggest that [it] has no limits" or "embraces every discovery." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 309 (1980). The legislative background of the 1952 Patent Act makes clear that "'anything under the sun that is made by man'" is "not necessarily patentable under section 101": all "the conditions" for patent protection must first be met. S. Rep. No. 1979, 82d Cong., 2d Sess. 5 (1952); see *Bilski*, 130 S. Ct. at 3249 (Stevens, J., concurring). In particular, a patent cannot preempt "laws of nature, physical phenomena, or abstract ideas":

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor

> could Newton have patented the law of gravity. Such discoveries are 'manifestations of * * * nature, free to all men and reserved exclusively to none.'

Chakrabarty, 447 U.S. at 309 (quoting *Funk Brothers Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)). This Court was therefore careful to explain that the "human-made, genetically engineered bacterium" it held patentable in *Chakrabarty* was "a product of human ingenuity," *not* a "natural phenomenon." 447 U.S. at 305, 309.

That this limitation on patentability is essential to promote innovation has long been understood. See *LeRoy* v. *Tatham*, 55 U.S. 156, 174-175 (1852) ("no one can appropriate * * * exclusively to himself, under the patent laws," a "principle," "fundamental truth," or "natural agenc[y]," because such monopolies "discourage arts and manufactures").[6] As this Court has explained, "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts" cannot support a patent monopoly because "they are the basic tools of scientific and technological work." *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972). As such they are "part of the storehouse of knowledge" and must be "free to all men." *Funk Brothers*, 333 U.S. at 130. That rule bars not only a patent claim aimed directly

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[6] The 1793 Patent Act defined patentable subject matter as "any new and useful art." Congress did not intend any substantive change when it replaced this phrase in 1952 with "any new and useful process" and defined "process" as "process, art, or method." See *Diehr*, 450 U.S. at 181-184; *Bilski*, 130 S. Ct. at 3248 (Stevens, J., concurring) ("the 1952 Act did not alter the nature of the then-existing limits").

at a natural phenomenon, but also one whose "*practical effect* would be a patent on the [phenomenon] itself," because such a claim also "wholly pre-empt[s]" use of the natural phenomenon. *Benson*, 409 U.S. at 71-72 (emphasis added). This Court's preemption decisions illustrate how these principles are applied, and show that Prometheus's claims fail the "natural phenomenon" standard.

2. In *Funk Brothers*, the inventor discovered that certain strains of bacteria that enable legume crops to thrive remained effective when combined. It patented a product of mixed bacteria cultures that would be more useful for growers than individual cultures. This Court held that although the inventor's steps applied a "law of nature" to a "new and useful end," they were not patentable because the essence of the product was a combination of natural biologic materials. 333 U.S. at 130.

The Court explained that the "qualities of these bacteria" are "manifestations of nature." 333 U.S. at 130. Even though the bacteria had been combined in a "new and different composition" that "contributed utility and economy," simply "aggregati[ng] species fell short of invention." *Id.* at 130-131. It was merely "an advance in the packaging" of the bacteria in which "[n]o species acquires a different use" and each "has the same effect it always had." That the combination was "an important commercial advance" did not satisfy the requirements of the Patent Act. "[O]nce nature's secret" that bacteria could be mixed without inhibiting their effectiveness was discovered, "the state of the art made the production of a mixed inoculant a simple step." *Id.* at 132. Attaching non-inventive production "steps" to a law of nature did not result in a patentable invention.

3. In *Benson*, this Court applied the same principles that governed the product claim in *Funk Brothers* to a "process" patent for the computer-based conversion of decimal numbers into binary numbers using generalized mathematical formulas. 409 U.S. at 64-65, 67-68. The method at issue introduced variations on "the ordinary arithmetic steps a human would use," employing an algorithm and existing computer technology. *Id.* at 67. Nevertheless, the Court held the patent invalid under Section 101 because it did not recite what was to be done with the numbers once they were converted. It used "[p]henomena of nature" and mathematical concepts in a "process" that was "so abstract and sweeping as to cover both known and unknown uses" of the conversion: any "end use" of the conversion was within its scope. *Id.* at 67-68. The "practical effect" was thus to "wholly preempt the mathematical formula," amounting to a patent on "the algorithm itself." *Id.* at 71-72.

4. This Court expanded upon these principles in *Parker* v. *Flook*, where the claims recited a process for updating an alarm limit for use in common chemical processes, employing a mathematical formula. The method consisted of three steps: measuring a variable in the chemical process, such as temperature, using an algorithm to calculate what the alarm limit should be, and adjusting the alarm limit to the new value. The algorithm was new, but the other steps were "well known." 437 U.S. at 585-586, 594.

The Court held that the claims failed to satisfy Section 101, even though they were narrower than the patents rejected in *Benson* in two ways. First, although the *Flook* claims covered "any use" of the

formula for updating alarm limits over a variety of chemical processes in particular industries, they left uses outside those industries in the public domain. 437 U.S. at 589-590, 592. Second, unlike the open-ended patent in *Benson*, they recited "useful, though conventional, post-solution applications" in the form of a final step that called for adjusting the alarm limit to the figure computed according to the formula. *Id.* at 585, 590.

These differences did not save the claims. To allow "conventional or obvious" post-solution activity to make a process based on natural laws patentable would "exal[t] form over substance." 437 U.S. at 590. A "competent draftsman" could make any mathematical formula patentable by attaching "post-solution activity." *Ibid.* Even the "Pythagorean theorem" could be patented by embedding it in a process containing "a final step indicating that the formula" could "be usefully applied to existing surveying techniques." *Ibid.* Because "the application, considered as a whole, contain[ed] no patentable invention" but consisted of "well known" steps plus a natural law, it did not satisfy Section 101. *Id.* at 594; see *ibid.* (a natural phenomenon "cannot support a patent" absent "some other inventive concept in its application").

5. Citing *Flook* and *Benson*, the Court in *Diamond* v. *Diehr*, 450 U.S. 175, 191-192 (1981), reaffirmed three important principles that govern analysis under Section 101: that "laws of nature" may not be claimed in the abstract, that this limitation "may not be circumvented" by focusing a claim on "a particular technological environment," and that "insignificant post-solution activity" cannot

"transform an unpatentable principle into a patentable process."

The claims in *Diehr*, in contrast to those in *Benson* and *Flook*, satisfied Section 101 because they narrowly confined use of the Arrhenius equation in a "process which, when considered as a whole, is performing a function which the patent laws were designed to protect"—transforming raw rubber into precision molded products. *Id.* at 184, 192. The claimant used the equation in a detailed step-by-step method that solved a significant industrial problem by continuously monitoring temperature inside a mold and using that data to open the mold only when the rubber was perfectly cured—"a result heretofore unknown in the art." *Id.* at 177-178, 184, 193 n.15. The claimant did not seek to preempt use of the equation generally, but only to foreclose its use "in conjunction with all of the other steps in their claimed process" in the particular application of molding raw rubber into finished products. *Id.* at 187.

6. *Bilski* reaffirmed the vitality of all these precedents. Although the process patent considered there made a contribution to knowledge by laying out a formula for risk arbitrage, applying the formula to specific industries, and then using random analysis techniques to establish inputs into the equation, this Court nonetheless disapproved it because it would "pre-empt use" of a "fundamental economic practice" that was "long prevalent" in the business world, and would "effectively grant a monopoly over an abstract idea." 130 S. Ct. at 3231. The patentee's efforts to "limit" the abstract formula to "one field of use" and add "token postsolution components" did not "make the concept patentable," or demonstrate that the

inventor created a "new and useful process" within the language of Section 101. *Id.* at 3225, 3231.

Justice Kennedy explained that this result strikes a balance that rewards "valuable inventions without transgressing the public domain." 130 S. Ct. at 3227. Care is especially necessary in considering method or process patents because they "raise special problems in terms of vagueness and suspect validity." *Id.* at 3229. "If a high enough bar is not set" for such patents, "patent examiners and courts could be flooded with claims that would put a chill on creative endeavor and dynamic change." *Ibid.* And Section 101's prohibition on patents that attempt to monopolize "abstract ideas" is particularly important in drawing the necessary line. *Id.* at 3229-3230.

Each of the Justices in *Bilski* agreed with these propositions. Justices Breyer and Scalia, concurring, observed that all members of the Court agree that incentives to innovation that "are worth to the public the embarrassment of an exclusive patent" must "outweigh the restrictive effect" of the patent monopoly. 130 S. Ct. at 3258. Federal courts must therefore exercise care "to determine not only what is protected, but also what is free for all to use." "Phenomena of nature, though just discovered," are "not patentable," and patentees may not "wholly preempt the public's access to the basic tools of scientific and technological work." *Ibid*; see *id.* at 3235 (Stevens, J., concurring). It is essential to consider whether a claimed process, "considered as a whole," is "performing a function which the patent laws were designed to protect." Courts must always reject overbroad and abstract patent claims that are "ridiculous" and "truly absurd," like patents on video

displays intended to teach the art of housekeeping. *Id.* at 3258-3259 (Breyer, J., concurring).

7. Under the settled principles described in *Funk Brothers*, *Benson*, *Flook*, *Diehr*, and *Bilski*, Prometheus's claims are invalid. See *Deepsouth Packing Co.* v. *Laitram Corp.*, 406 U.S. 518, 531 (1972) ("We would require a clear and certain signal from Congress before approving the position of a litigant" who "argues that the beachhead of privilege is wider, and the area of public use narrower, than courts had previously thought"). Like the claims disapproved in *Benson* and *Flook*, Prometheus's patents recite a natural phenomenon—the biological correlation between metabolite levels and health—without describing what is to be done with that phenomenon beyond considering whether a dosage adjustment may be necessary. Because Prometheus's claims culminate with this open-ended "mental step" (Pet. App. 21a), their "practical effect" is to "wholly preempt" use of the natural correlation across the entire spectrum of autoimmune diseases. *Benson*, 409 U.S. at 71-72. Prometheus concedes as much when it describes what others may and may not do without paying Prometheus:

- Physicians may freely use thiopurine metabolite correlations in patient care and research only if they take the impractical—and given the simplicity and ubiquitousness of blood tests, completely wasteful—step of developing "a method for measuring metabolite levels that does not require analysis of a bodily sample or a pre-treatment diagnostic test." Br. in Opp. 27.

- Mayo cannot consider the correlation—even if it "doesn't act on it"—in providing patient care or conducting research. 1JA 42.
- Mayo may not market its own less costly test based on improved metabolite ranges, which it believes enhances patient health and economy. *Supra*, pp. 8-10.
- Mayo researcher Dr. el-Azhary infringed when, knowing Prometheus's metabolite ranges, she determined that they were medically inappropriate for dermatology patients. *Supra*, pp. 11-13.

In contrast to *Diehr*, Prometheus did not recite a particular use of the correlation. As these examples show, its patents cover use of the correlation in every manner possible for *any* autoimmune disease. Its suggestion of certain metabolite ranges that it deems relevant should not preempt the right of others to think about the same biological correlation and form their own conclusions about the need for dosage changes. The abstract concepts Prometheus preempts are "part of the storehouse of knowledge of all men, free to all men and reserved exclusively to none." *Bilski*, 130 S. Ct. at 3225.

C. The Preemptive Effect Of The Patents Is Not Mitigated By The Token And Long-Prevalent Steps Recited By Prometheus.

For two independent reasons, Prometheus cannot defend its patents by dressing up this natural correlation as a "process" that includes additional steps that are "token," "conventional," long-prevalent," or "obvious." *Diehr*, 450 U.S. at 193 n.14; *Bilski*, 130 S. Ct. at 3231; *Flook*, 437 U.S. at 590.

First, the preparatory steps in some of Prometheus's claims—administering a drug and testing blood for metabolites of the drug—are "data-gathering" steps, as the district court found, and ordinary means of observing the natural correlation. Pet. App. 62a; see also *id.* at 23a (Federal Circuit acknowledged "prior steps" simply "provide useful information"); *In re Meyer*, 688 F.2d 789, 794 (C.C.P.A. 1982) (a "data gathering step" "cannot make an otherwise nonstatutory claim statutory"). Where "qualities are the work of nature," "packaging" them with steps that make no difference to the way the natural phenomenon operates is "not enough" to satisfy Section 101. *Funk Brothers*, 333 U.S. at 130-132.

Unlike the steps in the *Diehr* patent that narrowly confined the Arrhenius equation to use in a process for molding rubber, the data gathering steps in Prometheus's patents do *nothing* to narrow the range of preemption of the biological phenomenon. Any physician seeking to improve Prometheus's criteria inevitably would go through the same preliminary steps, which neither limit the scope of the claims nor prevent them from preempting all practical uses of the natural correlations. *Diehr* forbids the use of patent drafting that recites steps without confining the breadth of preemption of a law of nature. See 450 U.S. at 192.

A second defect in Prometheus's patents is that their administration and testing steps are "well known" and "long prevalent" in medical practice. *Flook*, 437 U.S. at 594; *Bilski*, 130 S. Ct. at 3231. Prometheus did not invent or make any contribution to either step. Nor was it the first to observe correlations between metabolite levels and dosage

adjustments, a concept familiar to physicians for decades. 2JA 1-3; *supra*, p. 4. Well-known, non-inventive steps cannot turn a natural phenomenon into patentable subject matter. See *Morton* v. *New York Eye Infirmary*, 17 F. Cas. 879, 882-883 (S.D.N.Y. 1862) (denying patent for the process of anesthetizing patients with ether because "[t]he effect discovered was produced by old agents, operating by old means upon old subjects. The effect alone was new," and as a law of nature "is not patentable"); *Flook*, 437 U.S. at 594-595 (combination of well-known chemical processes and monitoring practices with computer-applied algorithm "contains no claim of patentable invention").

These precedents do not improperly import novelty or obviousness analysis into Section 101 from Sections 102 and 103. Br. in Opp. 16; see *Flook*, 437 U.S. at 592 & n.14. Section 101 on its face limits patentable subject matter to a "new and useful process," making clear that if "the application, considered as a whole, contains no patentable invention" the provision is not satisfied. *Flook*, 437 U.S. at 591, 594. A "novel and useful structure" created by using a "scientific truth'" satisfies Section 101. But when, as here, "[t]he process itself' merely combines well-known steps with a law of nature and broadly preempts use of the latter, the result does not warrant a patent monopoly. *Id.* at 588, 591, 594. *Bilski* squarely holds that attaching "long prevalent" steps to an abstract idea or law of nature is insufficient. 130 S. Ct. at 3231.

Justice Breyer's dissent from the dismissal of *LabCorp* for procedural reasons (joined by Justices Stevens and Souter) illustrates the proper application of this Court's preemption precedents to

a patent like Prometheus's. The *LabCorp* patent involved several proposed "steps" to test a patient's body fluid to determine the level of amino acids and then correlate that level with a vitamin deficiency. As here, it sought to exert "control over doctors' efforts to use [a natural] correlation" through a "process" that the claimant urged was "useful, concrete, and tangible." 548 U.S. at 134, 136.

Justice Breyer explained, however, that the well-known testing steps in *LabCorp* were "nothing * * * that adds anything more of significance" to "an unpatentable 'natural phenomenon.'" 548 U.S. at 138. Embedding the correlation in a "process" was not enough to "avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge." *Id.* at 137-138. The process steps added nothing inventive. Nor did they limit the scope of the patent, which "any doctor" would "necessarily infring[e]" "merely by thinking about the relationship after looking at a test result." *Id.* at 132.

As Justice Breyer explained in *LabCorp*, any conduct can be described as a "process" with "a series of steps," but the key legal question is "what those steps embody." 548 U.S. at 137-138. Here, as in *LabCorp* and *Flook*, Prometheus's patents embody "a simple natural correlation" combined with well-known steps that do nothing to prevent the claims from wholly preempting physicians' use of that correlation. *Id.* at 136-137.[7]

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[7] In *LabCorp* the measured amino acids occurred naturally, while here the metabolites are the body's natural reaction to a drug. Prometheus did not invent the drug, and it concedes that

D. The Federal Circuit's Rote Reliance On The Machine-Or-Transformation Test Clashes With This Court's Precedents.

The Federal Circuit failed to follow this Court's precedents when it applied its "machine-or-transformation" test to uphold Prometheus's patents, reasoning that the administering and testing steps involve "transformations" of matter—*i.e.*, changes in the human body resulting from administration of drugs and changes in the blood when it is tested for metabolites. Pet. App. 17a-18a, 21a-23a. By making these well-known information-gathering steps into the touchstone of patent eligibility, the Federal Circuit misunderstood *Bilski*, which held that a "transformation" is a "clue" to patent eligibility—not a talisman—and does not override the principle that "laws of nature" must be free for all to use. 130 S. Ct. at 3225-3226.

Under this Court's preemption decisions, patentability is not an exercise in labeling. Recitations in a claim involving machines or transformations are relevant *if* they show that inventors have carved out a subset of real-world applications of a natural phenomenon, *e.g.*, by covering particular uses of the phenomenon on a particular machine (leaving open to the public other uses on other machines), or by using the phenomenon to transform something else (leaving open to the public other transformations). That is what happened in *Diehr*, where the patentee limited its claims to using the Arrhenius equation for a particular rubber molding process and left open its use in other applications. 450 U.S. at 187-188. The

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the difference between synthetic and natural promoters of a biologic change is immaterial. See Br. in Opp. 30 n.7.

transformations here, by contrast, are incidental to data-gathering, have no limiting effect on the claimed monopoly, and have no rational connection to the goals of the patent system.

Absent a focus on whether a machine or transformation narrows the field of preemption, the Federal Circuit's test is mechanical and easily manipulated, leaving courts and patent examiners without guidance and prone to arbitrary line drawing. The Federal Circuit's fractured decision in *Association for Molecular Pathology* v. *Myriad Genetics*, 2011 WL 3211513 (Fed. Cir. July 29, 2011), illustrates this point. Explaining in *Myriad* why it held that Prometheus's patents satisfy Section 101, the court observed that metabolite levels cannot be determined by inspection, only by "'extract[ing] metabolites from a bodily sample and determin[ing] their concentration'"—*i.e.*, testing blood as physicians long have done. *Id.* at *22. In denying the Myriad "method claims" directed to "'analyzing' or 'comparing'" a patient's BRCA gene sequence with the normal sequence to diagnose "the presence of cancer-predisposing mutations," the Federal Circuit contrasted the Prometheus "transformation" with Myriad's ability to compare genes "by mere inspection." *Id.* at *2, *22.

It is frankly absurd for the court to hold that the Myriad patents fail because they are "directed to the abstract mental process of comparing" two genes, while Prometheus's patents pass muster because considering the correlation between metabolites and patient health depends on conducting a blood test. BRCA genes cannot be inspected in the body. A segment of DNA must first be *extracted* from the patient and chemically isolated from its chromosom-

al environment. *Myriad*, 2011 WL 3211513, at *17, *20. That a physician's conclusions depend in one case on conducting standard blood tests and in the other on isolating and observing DNA extracted from the patient is a meaningless distinction. It says nothing at all about the scope of preclusion of a natural law, which is decisive under this Court's preemption decisions.

So arbitrary a test is no standard at all. Mayo's proposed approach, by contrast, explains how the machine-or-transformation inquiry identifies situations in which the patentee is not monopolizing all real-world applications of a natural phenomenon and will allow the PTO and courts to apply Section 101 consistently. See *Brenner* v. *Manson*, 383 U.S. 519, 532 (1966) (interpreting Section 101 "in light of the general intent of Congress, the purposes of the patent system, and the implications of a decision one way or the other").

E. Prometheus May Not Block Broad Areas Of Scientific Inquiry With Open-Ended Patents Built On A Narrow Discovery.

In addition to impermissibly preempting all uses of a natural phenomenon, Prometheus's patents violate Section 101 because they leverage a minimal contribution to medicine—attaching disputable numbers to a natural correlation—into a patent that blocks a broad area of scientific inquiry into the best way to treat a wide variety of serious diseases. The Act does not permit one who makes a narrow discovery to preempt future development in adjacent areas. See *Graham* v. *John Deere Co.*, 383 U.S. 1, 7-9 (1966) (Thomas Jefferson, author of the 1793 Patent Act "insist[ed] on a high level of patentability" that did not "gran[t] patents for small details").

Even Samuel Morse's monumental invention of electromagnetic telegraphy could not justify a broad patent precluding others from working on different forms of electronic communication, such as telephone and radio. *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 113-120 (1853). As Chief Justice Taney put it, "some future inventor, in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current" which is "less complicated—less liable to get out of order—less expensive in construction, and in its operation. But yet if it is covered by this patent the inventor could not use it, nor the public have the benefit of it without the permission of this patentee." *Id.* at 113. Stated otherwise, "indiscriminate creation of exclusive privileges tends rather to obstruct than to stimulate invention." *Atlantic Works* v. *Brady*, 107 U.S. 192, 200 (1883). It "creates a class of speculative schemers" who "watch the advancing wave of improvement, and gather its foam in the form of patented monopolies, which enable them to lay a heavy tax upon the industry of the country, without contributing anything to the real advancement of the art." *Ibid.*

In keeping with the need to avoid patent monopolies that interfere with the work of scientists beyond the scope of any specific invention, this Court in *Brennner* v. *Manson* denied a patent for a new chemical process for making steroids that were of scientific interest in the search for cancer therapy but that as yet had no known utility. 383 U.S. at 520-522, 529. In invalidating this process patent because it had not been "reduced to production of a product" that would "precise[ly] delineat[e]" the "metes and bounds of th[e] monopoly," the Court explained that patents may not

"engross a vast, unknown, and perhaps unknowable area," or "confer power to block off whole areas of scientific development without compensating benefit to the public." *Id.* at 534.

Like the patent rejected in *Brenner*, Prometheus's patents are vague and open-ended and do not set forth any real therapy—just an exhortation to consider a possible dosage change in the light of some numbers. But the monopoly effect of Prometheus's patents is sweeping. They prevent physicians and researchers from considering better metabolite ranges for different diseases or specific subsets of patients, or marketing a cheaper and more accurate test with different ranges. The patents would make Prometheus's metabolite ranges conclusive—"block[ing] off" "scientific development"—in a field where research is dynamic and ongoing. That result is not "clearly commanded by the statute" and should not be tolerated. *Brenner*, 383 U.S. at 534.

F. Upholding Prometheus's Patents Would Suppress Competition To The Detriment Of Patient Health.

Patent protection "reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance." *Bonito Boats* v. *Thunder Craft Boats*, 489 U.S. 141, 146 (1989). The challenge is to strike a "balance between protecting inventors and not granting monopolies over procedures" that foreclose "independent, creative application of general principles." *Bilski*, 130 S. Ct. at 3228 (Kennedy, J.). Open-ended patents like Prometheus's, which claim a broad monopoly with the drafting trick of embedding natural laws in a "process" that imposes no meaningful limitation on the claim, "decreas[e]

the range of ideas available as the building blocks of further innovation," in "conflict with the very purpose of the patent laws." *Bonito Boats*, 489 U.S. at 151.

Prometheus's patents must be considered "in light of this Nation's historical antipathy to monopoly and of repeated congressional efforts to preserve and foster competition." *Deepsouth Packing*, 406 U.S. at 530. The Federal Trade Commission has explained that careful gatekeeping in patent law is essential to foster the competition that is the goal of the Nation's antitrust laws. "Poor patent quality and legal standards"—including "claims that are likely overbroad"—have "anticompetitive effects," result in "unwarranted market power," and "unjustifiably increase costs," thereby "hamper[ing] competition that otherwise would stimulate innovation." FEDERAL TRADE COMMISSION, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY 5 (Oct. 2003) ("FTC 2003 REPORT"), available at http://ftc.gov/os/2003/10/innovationrpt.pdf.

To avoid these harms to consumers, it is important that "in interpreting the scope of patentable subject matter under Section 101," courts "ask whether granting patents on certain subject matter in fact will promote [scientific] progress" or instead "hinder competition that can effectively spur innovation." *Id.* at 15. See also FEDERAL TRADE COMMISSION, THE EVOLVING IP MARKETPLACE: ALIGNING PATENT NOTICE AND REMEDIES WITH COMPETITION 47-48 (Mar. 2011) ("FTC 2011 REPORT") ("questionable" patents "distort competition" and "inhibit innovation" by "discouraging firms from conducting R&D in areas the patent improperly

covers and raising costs through litigation and unnecessary licensing"; "[p]atent quality" is therefore "vitally important for achieving the balance of exclusivity and competition that best enhances consumer welfare"), available at http://ftc.gov/os/2011/03/110307patentreport.pdf.

"[C]ompetition from acceptable alternatives" limits a patentee's market power and "helps generate lower prices, more choices and higher quality products for consumers." FTC 2011 REPORT at 2. But when a claim is as vague and open-ended as Prometheus's that will never occur. Prometheus has squelched all competition to provide improved tests by claiming a monopoly on the correlation between thiopurine metabolites and health, as its suit against Mayo and attack on Dr. el-Azhary show. Far from "encourag[ing] investmen[t] in those inventions that are more likely to be valued by consumers," these patents distort competition by cutting off pro-consumer development of better and cheaper tests, including tests directed to other diseases. And no monopoly was necessary to incentivize the research that led to Prometheus's patents. Canadian physicians did what doctors always have done—looked at medical databases and reached conclusions about how to treat patients in light of them. Prometheus simply bought the right, after the fact, to patent their conclusions.

In short, Prometheus's patents have "commandeered the entire market" by monopolizing all thought about the health effects of the biologic fact, well known to physicians for many years, that thiopurine drugs produce metabolites that relate to the health of patients with autoimmune diseases. CHRISTINA BOHANNAN & HERBERT HOVENKAMP,

CREATION WITHOUT RESTRAINT: PROMOTING LIBERTY AND RIVALRY IN INNOVATION ch. 5, at 29 (forthcoming 2011); see *ibid.* ("Inventions that are nothing more than verbal assertions * * * cover as wide a market as human language allows"). By "creating a monopoly in a rather common mechanism" that physicians and researchers "have thought of entirely on their own," Prometheus's patents operate as "bottlenecks on innovation competition" that "prevent other firms from *independently* developing competing processes or products." *Id.* ch. 5, at 5, 27, 29.[8]

G. Prometheus's Patent Claims Are Not The Sort Of "Invention" Congress Meant To Protect.

Given the settled precedents and principles we have described, Prometheus's contention that it should be able to monopolize the natural correlation between thiopurine metabolites and health "should be addressed to the political branches of Government, the Congress and the Executive, and not to the courts." *Chakrabarty*, 447 U.S. at 317. If laws of nature long known to medical science "are to be patentable, considerable problems are raised" for medical research and patient care that "only committees of Congress can manage." *Benson*, 409 U.S. at 73; see *Flook*, 437 U.S. at 595-596 ("we must proceed cautiously when we are asked to extend patent rights into areas wholly unforeseen by Congress"; the "[d]ifficult questions of policy" involved must "be answered by Congress"). Far from

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[8] With the authors' permission, petitioners have sought leave to lodge with the clerk page proofs of the cited chapter of this forthcoming book.

citing a "clear and certain signal from Congress" that expansion of patent protection is proper (*id.* at 596), Prometheus has offered no evidence whatsoever that its attempted patent on medical judgment is something "which the patent laws were designed to protect." *Diehr*, 450 U.S. at 192.

To begin with, the legal principles upon which we rely—that a patent may not preempt laws of nature or abstract ideas, and that it is not saved by embedding the law of nature in a well-known process that does not narrow the scope of the claim—were well established before Congress recodified the Patent Act and enacted Section 101 in its current form in 1952. Congress at that time intended no substantive change in the law. See *supra*, p. 27 & n.6.

Equally well established was the legal principle that federal legislation must be construed to avoid conflict with First Amendment freedoms whenever possible. See *Edward J. DeBartolo Corp.* v. *Florida Gulf Coast Bldg. & Constr. Trades Council*, 485 U.S. 568, 574-575 (1988) (observing that this "cardinal principle" has "for so long been applied by this Court that it is beyond debate"); *New York* v. *Ferber*, 458 U.S. 747, 769 n.24 (1982). Throughout our Nation's history, the freedom to think—to consider what one has seen, to reach mental conclusions based on those observations, and to change one's future plans in light of those conclusions—has been deemed sacrosanct. Reflecting that tradition, this Court held in *Ashcroft* v. *Free Speech Coalition*, 535 U.S. 234, 253 (2002), that speech is protected from government restriction because "[t]he right to think is the beginning of freedom, and speech must be protected

from the government because speech is the beginning of thought."

Prometheus's sweeping claims chill important research and speech in ways that Congress never would have intended. As the American Medical Association explained in urging review, patents like Prometheus's entangle physicians in "a vast thicket of exclusive rights" to "basic diagnostic information" that is "critical" to "providing sound medical care," to "the detriment of the nation's health." Am. Br. of American College of Medical Genetics, *et al.*, ("AMA Br."), at 5-6, 20-21. That chilling effect is obvious here, where Prometheus deposed Dr. el-Azhary, accusing her of infringement because she conducted research on the appropriate metabolite range for dermatology patients while aware of Prometheus's range, and where Dr. el-Azhary dared not publish her conclusion that Prometheus's range was defective for dermatology patients until after the district court invalidated Prometheus's patents. See ACLU Am. Br. in *Bilski*, No. 2007-1130 at 5-7, 14 (Fed. Cir. Apr. 3, 2008), available at http://www.aclu.org/pdfs/freespeech/in_re_bilski_aclu_amicus.pdf (patents like those here and in *LabCorp* amount "to a patent on pure thought or pure speech"; courts "should interpret patent law doctrines" to "avoid the difficult application of First Amendment doctrines").

Prometheus's patents, deferring to a physician's medical judgment, while demanding payment for exercising that judgment, are even more ridiculous than the example cited in *Bilski* of teaching good housekeeping. *Supra*, pp. 32-33. It is unthinkable that Congress intended the patent laws to embargo independent research and thought about a natural correlation based on someone's suggestion of

numbers that he deems relevant, but which others may reasonably reject. See *Microsoft Corp.* v. *i4i Ltd. P'ship*, 131 S. Ct. 2238, 2253 (2011) (Breyer, Scalia, Alito, JJ., concurring) (rigorous judicial scrutiny is required to assure "that discoveries or inventions will not receive legal protection where none is due"). This Court should not presume that Congress intended such a harmful result.

II. PATENTS ON MEDICAL CORRELATIONS WILL SUPPRESS RESEARCH AND INNOVATION, INTERFERE WITH PATIENT CARE, AND INCREASE COSTS.

The holding below that patents may be awarded on correlations between the administration of medication and the resulting biological reaction is flatly inconsistent with this Court's precedents. But more than that, such patents are far more likely to retard than to advance innovation, and thus to frustrate the broader goals of federal patent law. In fact, patents on natural medical correlations of the sort granted in this case can be expected to have a host of pernicious consequences: such patents will suppress both basic research and specific advances in medical treatment; interfere with patient care and the exercise of medical judgment by physicians; and raise consumer costs. These considerations confirm that the decision below should be reversed.

1. To begin with, the likely effect of a patent on innovation and competition has an important bearing on the patent's validity. The Court has repeatedly emphasized that the "Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Bonito*

Boats, 489 U.S. at 146. See *Bilski*, 130 S. Ct. at 3228 (Kennedy, J.); *id.* at 3252 (Stevens, J., concurring in the judgment). Thus, "[t]he underlying policy of the patent system [is] that 'the things which are worth to the public the embarrassment of an exclusive patent,' * * * must outweigh the restrictive effect of the limited patent monopoly." *Bilski*, 130 S. Ct. at 3258 (Breyer, J., concurring in the judgment).

In a comprehensive review of the patent process, the Federal Trade Commission concluded that, "properly interpreted," patent law awards patents "only when necessary to provide incentives for inventions, their commercial development, or their disclosure." FTC 2003 REPORT, at 4. "If the promise of patent protection is not necessary for those purposes, however, then the costs—which may include higher prices or retarded follow-on innovation—may cause unjustified injury to consumers." *Id.* at 8. Against this background, "a heavy burden of persuasion should be placed upon those who would extend such protection." Stephen Breyer, *The Uneasy Case for Copyright*, 84 HARV. L. REV. 281, 322-323 (1970) (citing research in patent and copyright fields). Prometheus cannot meet that burden here: its patents are certain to "impede rather than 'promote the Progress of Science and useful Arts.'" *LabCorp*, 548 U.S. at 126-127 (Breyer, J., dissenting).

2. Patent protection assuredly is unnecessary to encourage research and innovation of the sort reflected in the Prometheus patents. Patents doubtless serve an important purpose "when the original innovator's efforts entail substantial fixed costs, and the imitators can copy the innovation cheaply." FTC 2003 REPORT, at 4. An example is the development of a new pharmaceutical or medical

device, which must be invented, tested, and approved, typically all at great expense. See *Bilski*, 130 S. Ct. at 3253 (Stevens, J., concurring in the judgment); Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 505 (2009).[9] But as the American Medical Association and other leading groups of physicians and medical colleges observed in supporting the grant of certiorari here, "[p]atents on scientific observations underlying medical care" lack "these salutary effects." AMA Br. at 9. "Development costs for these diagnostic tests" are "low, in part because approval of such tests does not involve the high regulatory costs involved in the development of pharmaceuticals and medical devices." *Id.* at 15. And the simple observation of medical correlations plainly "does not entail the same kinds of risk as does more traditional, technological innovation. It generally does not require the same enormous costs in terms of time, research, and development." *Bilski*, 130 S. Ct. at 3254 (Stevens, J., concurring in the judgment).

Moreover, as the Secretary of Health and Human Services' Advisory Committee on Genetics, Health, and Society ("the Secretary's Advisory Committee")

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[9] "Empirical analysis of the patent system is, at best, ambiguous as to the importance of this incentive except in certain specific industries, such as pharmaceutical products." John H. Barton, *Patents and Antitrust: A Rethinking in light of Patent Breadth and Sequential Innovation*, 65 ANTITRUST L.J. 449, 453 (1997). "[I]n most industries, patenting is among the less important mechanisms for protecting the results of innovation." BOHANNAN & HOVENKAMP, *supra*, ch. 5, at 4; see *id.* at 3 ("Time and first mover-advantage often provide greater or more predictable returns to innovation than patenting does").

recently noted in the area of genetic research, "[t]he prospect of patent protection" does not play a significant role in motivating scientists to conduct medical research. "Scientists typically are driven instead by factors such as the desire to advance understanding, the hope of improving patient care through new discoveries, and concerns for their own career advancement." GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS 1 (April 2010) ("ADVISORY COMMITTEE REPORT"), available at hhttp://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf.

Nor is the prospect of obtaining a patent necessary to support such work financially: the federal government "is likely the major funder" for basic research. *Id.* at 2; see John H. Barton, *supra*, 65 ANTITRUST L.J. at 453-454 ("nations have usually encouraged such research by direct support rather than by use of the patent system"). Similarly, patents "are not needed to stimulate the disclosure of research discoveries," because "[t]he norms of academic science encourage disclosure of research results, and scientists have strong incentives to publish and present their discoveries." ADVISORY COMMITTEE REPORT 2; see *id.* at 90.

These observations about the limited role of patents in encouraging medical research are not theoretical. The Secretary's Advisory Committee "found *no* cases in which possession of exclusive rights was necessary for the development of a particular genetic test, including test kits and tests for both common and rare genetic diseases." ADVISORY COMMITTEE REPORT 2 (emphasis added). And "exclusive rights do not result in faster test

development. In none of the cases studied was a patent-protected test the first to market." *Ibid.*

In the particular context here, the AMA and other medical groups have explained that "patents are not needed to incentivize physicians and researchers to study the kinds of clinical correlations at issue." AMA Br. 14-15. Indeed, the work behind Prometheus's patents was done by physicians who only later sold the right to patent their research to Prometheus at a minimal price. It is no exaggeration to say that Prometheus invested in litigation, not research. Given the certainty that such research will proceed without the promise of monopoly profits, the Prometheus patents "have not furthered innovation one bit but have only created a power to exclude from an otherwise competitive market." BOHANNAN & HOVENKAMP, *supra*, ch. 5, at 1.

3. That such patents are unnecessary is only half the problem; patents like those issued to Prometheus are certain to *inhibit* innovation and the improvement of patient care. That is true in several respects.

First, as a general matter, allowing patents to preempt important fields of research will retard innovation and increase costs. The rule against patenting fundamental scientific principles reflects both "'the enormous potential for rent seeking that would be created if property rights could be obtained'" in these basic principles and "'the enormous transaction costs that would be imposed on would-be users.'" *LabCorp*, 548 U.S. at 127 (Breyer, J., dissenting) (quoting WILLIAM LANDES & RICHARD POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 305 (2003)). When such patents are claimed—and this surely is true of the

Prometheus patents—the "monopoly breadth is a function of [the patent's] *lack* of technical specification." BOHANNAN & HOVENKAMP, *supra*, ch. 5, at 27. Unlike "[t]actile inventions," which "generally have alternatives," it is impossible to invent around "[i]nventions that are nothing more than verbal assertions" like those at issue here. *Id.* at 29.

This reality has significant real-world consequences. The holder of such a patent on a scientific principle or correlation "may be able to use it to threaten litigation and to bully competitors." *Bilski*, 130 S. Ct. at 3257 (Stevens, J., concurring in the judgment). This may lead other researchers "to forgo R&D in the areas that the patent improperly covers. * * * Such effects deter market entry and follow-on innovation by competitors and increase the potential for the holder of a questionable patent to suppress competition." FTC 2003 REPORT, at 5-6; see *id.* at 20 (such patents "create a 'significant drag' on competition" and "have a 'chilling effect on both public and private sector research'"). Academic commentary confirms that "use of a patent to prevent future research turns the research encouragement goal of the patent system on its head, and seems inherently anticompetitive as well." Barton, *supra*, 65 ANTITRUST L.J. at 454.[10]

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[10] See, *e.g.*, JAMES BESSEN & MICHAEL MEURER, PATENT FAILURE 8-9, 17, 27 (2008) (patents on "mental correlations" make it "very difficult to know [the patents'] boundaries," creating the "nee[d] to check a very large number of patents," inviting "disputes and litigation," and encouraging "patent trolls" to "opportunistically take advantage of poor patent notice to assert patents against unsuspecting firms"); DAN BURK & MARK LEMLEY, THE PATENT CRISIS AND HOW THE COURTS CAN SOLVE IT 123-124 (2009) (innovators must be able to work out

Second, these limiting effects on research and innovation are especially acute in the medical field, for reasons made apparent by the Prometheus patents themselves. It is fundamental that "[r]eady access to basic facts, such as a relationship between levels of drug metabolites and the drug's efficacy and toxicity, is essential to medical research," as knowledge about the effectiveness of specific treatment "accumulates through medical practice and is shared throughout the medical community." AMA Br. 13-14. But under the Prometheus patents, as the AMA and other medical groups explained, a physician or researcher "would become an infringer if he or she *merely considered what to do about the results [of a test of metabolite levels] in light of relevant scientific information*," while a laboratory would induce infringement simply "by publishing articles or brochures discussing the correlation" between those levels and drug efficacy. *Id.* at 11 (emphasis added). If these patents are valid, others can, and surely will, claim patent monopolies on scientific observations

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new uses of abstractions and natural phenomena "without fear of patent liability" because patents "cove[r] entire concepts"); LAWRENCE LESSIG, THE FUTURE OF IDEAS 205-217 (2001) (describing negative impact of broad patent protection on innovation; "we should be most concerned when existing interests use the legal system to protect themselves against innovation"); Robert Merges & Richard Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 915 (1990) ("[T]he real threat of a patent like this stems from the industry's close ties to science. * * * The Patent Office and courts should not permit the over-privatization of the scientific knowledge that makes the industry possible"); Andrew Torrance & Bill Tomlinson, *Patents and the Regress of Useful Arts*, 10 COLUM. SCI. & TECH. L. REV. 130, 138, 162-167 (2009) (collecting economic research showing lack of stimulus to innovation from broad patent grants).

underlying proper diagnosis and treatment of a host of medical conditions.

As we have explained, patents on scientific correlations "often claim (or come close to claiming) fundamental principles of nature; therefore, it is frequently not possible to invent around these patents to produce materials of equivalent diagnostic and research value." ADVISORY COMMITTEE REPORT 90. Necessarily, such patents

> discourage research by impeding the free exchange of information, for example by forcing researchers to avoid the use of potentially patented ideas, by leading them to conduct costly and time-consuming searches of existing or pending patents, by requiring complex licensing arrangements, and by raising the costs of using the patented information, sometimes prohibitively so.

LabCorp, 548 U.S. at 127 (Breyer, J., dissenting)

Here, too, as the Secretary's Advisory Committee explained in detail, "[t]hese concerns are more than hypothetical. Patents are already hindering the development" of genetic tests and laboratories "are already choosing not to report medically significant results * * * for fear of liability." ADVISORY COMMITTEE REPORT 3. There also "is evidence to suggest that patents on genes discourage follow-on research." *Id.* at 2. See *id.* at 89; Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Non-problem? Rethinking the Anticommons in Biomedical Research*, 45 HOUS. L. REV. 1059, 1071 (2008) ("Empirical evidence in the United States suggests that patents on genes have impeded both the provision of genetic testing services and the

development of new tests by diagnostic laboratories"). Indeed, the Prometheus patents have had precisely that effect in this case, precluding Mayo researchers from developing improved metabolite ranges and interfering with Dr. el-Azhary's effort to establish therapeutic ranges for skin disorders that are not addressed by the research underlying the Prometheus patents. Patents that have such an effect are demonstrably "less an incentive to basic research than a barrier to applied research." Barton, *supra*, 65 ANTITRUST L.J. at 454.[11]

Third, in addition to undermining medical research, the Prometheus patents (and the many others like them that would follow if these patents are upheld) will have an immediate adverse effect on the quality of patient care, increasing the cost and reducing the availability of medical service. "It is a routine part of the practice of medicine—indeed, it is essential to meet appropriate medical standards of care—for physicians to monitor metabolite levels and to use those levels along with other laboratory and clinical parameters to guide dosage adjustments." AMA Br. 10. That being so, allowing a single patent

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[11] The point is confirmed by Prometheus's own defense of its patents, which asserts that they will not freeze research because scientists remain free to develop "a method for measuring metabolite levels that does not require analysis of a bodily sample." Br. in Opp. 27. Even assuming that such an unlikely, hands-free metabolite measurement method could be developed (and it is hard to imagine what such a method would entail; see 1JA 42-43), Prometheus recognizes that, at a minimum, its patents will require researchers to forgo use of the ordinary tools of medical testing and instead develop what would otherwise be a novel and wholly unnecessary alternative test, a process that would be inordinately expensive and inefficient.

holder to control the use that is made of such basic and essential medical observations will "raise the cost of medical care prohibitively without compensating benefits to medical research." *Id.* at 20.

Again, that effect is visible in this case: the Prometheus patents will bar Mayo physicians from offering a test of metabolite levels that is much less expensive than Prometheus's test and provides a more accurate and helpful correlation range to guide treatment. See Aaron S. Kesselheim & Michelle M. Mello, *Medical-Process Patents—Monopolizing the Delivery of Health Care*, 355 NEW ENG. J. MED. 2036, 2036 (2006) ("Medical-process patents threaten to complicate medical practice, increase costs, and restrict access to therapeutic and diagnostic procedures"); Lori Andrews, *et al.*, *When Patents Threaten Science*, 314 SCIENCE 1395, 1396 (2006) ("Although the discoveries of natural phenomenon may be necessary precursors to invention, improperly tying up these discoveries with patent rights will only drive up the costs of such subsequent innovations, if not thwart them altogether").

This case is hardly unique. Patient care and "access to tests" have "suffered in a number of ways" from patents that purport to control natural phenomena. ADVISORY COMMITTEE REPORT at 3. The sharply increased costs produced by giving monopoly control over a basic medical methodology has caused patients to "forgo testing because they cannot afford the test," or forgo "second-opinion testing from an independent laboratory." *Ibid.* And control of the use that can be made of medical correlations by a patent-protected sole provider raises "significant concerns about the quality" of test results because "[t]he most robust method for assuring quality in laboratory

testing is through the comparison of results obtained on samples shared between different labs." *Id.* at 4. In all, as Justice Breyer observed in *LabCorp*, 548 U.S. at 138, patents like those in this case

> may inhibit doctors from using their best medical judgment; they may force doctors to spend unnecessary time and energy to enter into license agreements; they may divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations; they may raise the cost of health care while inhibiting its effective delivery.

For these same reasons, the decision below cannot be reconciled with the ethical duties of physicians. As explained by the AMA and other medical organizations (AMA Br. 9-11), patent protection of Prometheus's claims conflicts with ethical standards that require physicians to spread knowledge—and improve diagnostic criteria—for the benefit of all. Prometheus acknowledges as much, agreeing that "physicians in the course of patient care are less able to avoid patent infringement than professionals in other fields, because avoiding the patented method may be inconsistent with the physician's ethical obligations." Br. in Opp. 34. Prometheus would solve this ethical dilemma by requiring physicians and patients "to pay inventors" —which is to say, Prometheus. *Id.* at 35. The better solution, and the one compelled by fundamental principles of patent law, is to hold that a putative patentee may not monopolize basic biological relationships at all.

CONCLUSION

The judgment of the court of appeals should be reversed.

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RESPONDENT'S BRIEF

No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

PETITIONERS,

v.

PROMETHEUS LABORATORIES, INC.,

RESPONDENT.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE RESPONDENT

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QUESTION PRESENTED

Whether the Federal Circuit correctly held that concrete methods for improving the treatment of patients suffering from autoimmune diseases by using individualized metabolite measurements to inform the calibration of the patient's dosages of synthetic thiopurines are patentable processes under 35 U.S.C. §101.

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INTRODUCTION

Mayo's brief distorts the record and ignores the Federal Circuit's unchallenged construction of the patents-in-suit.[1] Prometheus's claims are not drawn to scientific facts in the abstract, and they do not "preempt" broad principles like the laws of chemistry or the idea of measuring metabolites.[2] No one can infringe these claims merely by thinking about correlations. The claims describe concrete and specific physical processes, employing synthetic drugs and machines, that are used only to improve the clinical treatment of seriously ill patients.

Mayo argues that the claims' physical steps should be disregarded because they were old in the art, but that is precisely the discredited "point-of-novelty" approach to 35 U.S.C. §101 that this Court flatly rejected thirty years ago in *Diamond v. Diehr*, 450 U.S. 175 (1981), and again recently in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). This Court has made clear that a process must be evaluated for patent eligibility under §101 *as a whole*. Novelty and non-obviousness are distinct, fact-intensive questions that are not before this Court. And there certainly is no reason, at the dawn of the 21st century, for this Court to adopt special rules that would render personalized medicine

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[1] Petitioners Mayo Collaborative Services, which does business as Mayo Medical Laboratories ("Mayo Labs"), a for-profit commercial laboratory, and its affiliated non-profit co-defendant Mayo Clinic Rochester ("Mayo Clinic") are referred to herein collectively as "Mayo" unless otherwise specified.

[2] Respondent Prometheus Laboratories Inc. is referred to herein as "Prometheus."

inventions, or other processes designed to produce useful information, uniquely unpatentable under §101.

The Federal Circuit correctly held that the patents-in-suit are "squarely" patent-eligible "processes." This Court should affirm.

STATEMENT

A. Factual Background

Because this petition arises from Mayo's motion for summary judgment, all of Prometheus's "evidence ... is to be believed, and all justifiable inferences are to be drawn in [its] favor." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986).

1. *The Medical Problem.* Immune-mediated gastrointestinal disorders, such as Crohn's disease and ulcerative colitis, are incurable conditions that afflict millions of individuals. 2JA7.[3] Patients with these disorders suffer from debilitating symptoms and complications, including arthritis, anemia, rectal bleeding, diarrhea, abdominal pain, liver disease, skin ulcers, colon carcinoma, and intestinal cancer. 2JA7, 9-10. Although physicians have long treated these disorders with powerful corticosteroids to provide short-term relief from acute symptoms, such drugs cannot be used to control the disorders on a long-term basis without risking serious side effects. *See, e.g.*, Dkt.141 at 398; Barbara S. Kirschner, *Safety of Azathioprine and 6-Mercaptopurine in Pediatric Patients with Inflammatory Disease*, 115 Gastroenterology 813, 813 (1998); Daniel H. Present et

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[3] "_JA___" refers the Joint Appendix; "Pet.App.___" refers to the Petition Appendix; "CA_____" refers to the Joint Appendix in the Court of Appeals; and "Dkt.___" refers to the District Court docket.

al., *6-Mercaptopurine in the Management of Inflammatory Bowel Disease: Short- and Long-Term Toxicity*, 111 Annals of Internal Med. 641, 641 (1989).

These autoimmune disorders can also be treated effectively with synthetic thiopurine compounds, such as 6-mercaptopurine (6-MP) and azathiopurine (AZA), which transform inside the body into metabolites that suppress the patient's immune system and mitigate the symptoms. 2JA7, 10-11; 1JA25-27, 31-32. If administered in appropriate dosages, thiopurines are a safe and effective option for many patients, allowing doctors to avoid or minimize the need for potent steroids. *See* 1JA31.

The practical problem addressed by the patents-in-suit is determining the proper thiopurine dose for each patient. Because of variations in the activity level of the enzyme that breaks down these drugs (thiopurine methyltransferase, or TPMT), everyone metabolizes thiopurines differently. 2JA7. If a dose turns out to be too high for a particular patient, it could cause severe, potentially fatal, side-effects. 2JA7, 12, 25. Even "minimal doses" can be fatal for a minority of the population. 1JA26; 2JA7. These risks typically led doctors who used thiopurines to start with a very low dose and work slowly upwards while continually monitoring and testing their patients' blood and liver for toxicity. *See, e.g.*, Sanjoy Banerjee & Warren P. Bishop, *Evolution of Thiopurine Use in Pediatric Inflammatory Bowel Disease in an Academic Center*, 43 J. Pediatric Gastroenterology & Nutrition 324, 328-29 (2006). This "start low, go slow" approach multiplied office visits and costs and dramatically delayed the drug's effectiveness. *See* Marla C. Dubinsky et al., *A Cost-Effectiveness Analysis of Alternative Disease*

Management Strategies in Patients with Crohn's Disease Treated with Azathioprine or 6-Mercaptopurine, 100 Am. J. Gastroenterology 2239, 2243-45 (2005). And doctors still risked toxic consequences if they overshot the appropriate dosage for a particular patient. Many physicians, accordingly, were reluctant to treat their patients with thiopurines despite the potential benefits. 2JA7; 1JA31; Present, 111 Annals of Internal Med. at 641.

Researchers appreciated, in theory, that determining a patient's thiopurine metabolite levels could provide valuable information about the efficiency with which that patient metabolizes the drug. 2JA10. And laboratories had the technology to determine those metabolite levels from blood or bodily samples. 2JA11. But developing and validating a metabolite-based treatment protocol proved difficult because the complex metabolic pathways at issue were not completely understood. *See, e.g.*, 1JA26; Dkt.502 McClenahan Decl. Ex. I at 60.

Once administered, thiopurines are converted within the body into various metabolites, including 6-thioguanine (6-TG),[4] which is thought to be the active metabolite, and 6-methyl mercaptopurine (6-MMP). *See* 2JA7, 11; 1JA31; Dkt.45 at 194. In 1996, researchers at Hôpital Sainte-Justine in Montreal, led by Drs. Ernest Seidman and Yves Théorêt, concluded that measuring the level of those two metabolites in red blood cells can permit doctors to assess "responsiveness to treatment" in patients with gastrointestinal autoimmune disorders. Dkt.502

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[4] For purposes of this brief, 6-TG also refers to 6-thioguanine nucleotides (6-TGN). *See* Pet.App.3a n.1.

McClenahan Decl. Ex. I at 65; *see* 2JA1, 10; Dkt.43 at 128. After additional clinical research, they identified certain metabolite levels as useful targets for calibrating the treatment of these patients. In particular, they determined that a dose that results in a level of 6-TG between 230 and 400 picomoles (pmol) per 8×10^8 red blood cells and a level of 6-MMP below 7000 pmol per 8×10^8 red blood cells should be therapeutically effective and nontoxic. *See* 2JA10-13, 16-18; *see also* Dkt.45 at 194-95 (discussing 1995-1998 study period). Based on that research, Seidman and Théorêt filed a provisional patent application on improved treatment methods in 1998. *See* 2JA1, 19. The patents-in-suit both stem from that application.

No evidence in this record supports Mayo's suggestion (at 21) that, when that application was filed, doctors were already using measured metabolite levels clinically to calibrate thiopurine dosages for patients suffering from autoimmune disorders. To the contrary, at the time, there was persistent skepticism about whether monitoring metabolite levels would improve patient treatment. In 1997, for example, Mayo's own Dr. Sandborn wrote that "measurement of [red blood cell] 6-TGN and 6-MMP in patients with Crohn's disease treated with AZA or 6-MP remains investigational and cannot be recommended for routine clinical use." Dkt.43 at 128.[5] It was not until 1999,

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[5] *See also, e.g.*, Dkt.43 at 128 (1997 editor's note) (future studies needed to conclusively "establish a 'therapeutic window'"); Dkt.44 at 252 (declaration of Dr. Stephan R. Targan ¶ 7) (noting "skepticism of experts"); Dkt.16 at 300 ("[6-TG] target levels remain controversial"); Dkt.43 at 151 (2004 Sandborn article) ("routine determination" of such metabolites remains a "debated topic").

when Prometheus introduced its test, that metabolite measuring tests became commercially available to practicing gastroenterologists. Dkt.45 at 190-91.

2. *Prometheus's Claimed Treatment Methods.* When Seidman and Théorêt were awarded the patents-in-suit on their new treatment methods they assigned them to their employer hospital. *See* Pet.App.2a-5a; 2JA1-18 (No. 6,355,623, "the '623 patent"); 2JA19-35 (No. 6,680,302, "the '302 patent").[6] And the hospital granted an exclusive license to Prometheus, a pharmaceutical and diagnostic company that specializes in the development and commercialization of products that help physicians treat gastrointestinal autoimmune disorders. Pet.App.2a; CA12596.[7]

The various asserted claims in the two patents differ in certain respects, but all describe similar multi-step processes for improving the thiopurine-based treatment of patients suffering from autoimmune diseases by using metabolite measurements to help calibrate optimal doses. *See* 2JA16-18, 34-35.[8]

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[6] Although the actual motivations of the inventors in this case are irrelevant, nothing in the record supports Mayo's counter-intuitive conjecture (at 5) that they and their employer, which licensed their patents, were not motivated at all at the outset by the possibility of obtaining licensing fees.

[7] A redacted version of the license agreement is under seal in the district court. Dkt.275 Ex.H. No party or court has disputed that Prometheus has all substantial rights necessary to maintain this suit. *Cf.* U.S. Br. 5 n.2.

[8] Prometheus only asserted certain independent claims ('623 patent claims 1, 7, 22, 25, and 46, and '302 patent claim 1) and certain dependent claims ('623 patent claims 6, 14, 24, 30, 32, 33, 35, 36 and 53) in this litigation. *See* Pet.App.6a. Hereafter, any

First, most of the claims begin with the administration of a thiopurine compound to a patient with an autoimmune disorder. As noted, the thiopurine converts within the body into metabolites that do not otherwise exist in nature. 1JA26.[9]

Second, the patient's metabolite levels are determined. Because "metabolite levels are not detectable in raw human tissue," all methods for measuring their concentration require "significant chemical and physical alteration of blood or human tissue" and sophisticated laboratory equipment and machines. 1JA29-31, 42-43; 2JA11. Some of the dependant claims, for example, specify the use of high pressure liquid chromatography (HPLC), which entails an intricate series of operations on the blood (including heating, centrifuging, separating, and adding various reagents), running the resulting solution through a computer-controlled chromatography instrument, calculating the peak height or peak area, and feeding those figures into an equation, which finally outputs the metabolite levels. 1JA29-30.

Third, the metabolite measurements are compared to the patents' reference levels, "warning" the physician about the potential efficacy or toxicity of the patient's dosage. Pet.App.21a.

Claim 1 of the '623 patent is representative of the three-step claims at issue. It recites:

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discussion of the patents is limited to the asserted claims unless otherwise noted.

[9] Claim 46 of the '623 patent, and its associated dependent claims, omit that first "administering" step and start with the second step: "determining" the metabolite levels "in a subject administered a [thiopurine] drug ..., said subject having said immune-mediated gastrointestinal disorder." 2JA18.

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

2JA16.

The patents' various dependent claims further limit the methods to treatment with specified thiopurine compounds (such as AZA), using specified methods for determining metabolite levels (such as HPLC), and determining the results in specified measurement units (such as red blood cells). *E.g.*, 2JA16-17 (cl. 6, 32).[10] The patents do not claim the use of other drugs (such

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[10] Other *un*asserted claims limit the methods to the treatment of certain classes of patients (children) or certain autoimmune disorders (such as collagenous colitis) or to the consideration of certain toxic side-effects (such as hepatic toxicity). *E.g.*, 2JA16-17 (cl. 9, 10, 12).

as steroids) to treat autoimmune diseases or the use of thiopurines to treat other diseases (such as breast cancer or leukemia).

Since their introduction, Prometheus's patented methods have improved the lives of countless individuals suffering from autoimmune diseases. *See, e.g.*, Banerjee & Bishop, 43 J. Pediatric Gastroenterology & Nutrition at 326-29. With these tools, doctors are both more willing and better able to treat patients effectively with thiopurines and minimize resort to more toxic or less effective drugs.

The patented test, moreover, is both cost-effective and readily available. Hospitals and physicians wishing to use Prometheus's PROMETHEUS Thiopurine Metabolites test (formerly known as the PROPredictRx® Metabolites test) send Prometheus a blood sample, and Prometheus provides the results of the test with a risk assessment based on the metabolite levels. *See* 2JA36 (sample test results form). The test costs about $260. 1JA28. One study found that use of the test reduces net thiopurine treatment costs by about 10% (about $700 per patient in the first year) and reduces the time to effectiveness by about 14% (nearly four weeks). Dubinsky, 100 Am. J. Gastroenterology at 2245 tbl.5 (2005).

3. *Mayo's Competing Commercial Test.* Mayo is a substantial Prometheus customer, purchasing and using Prometheus's patented test over 17,000 times between 1999 and 2007. Pet.App.5a-6a; 1JA28; Pet. Br. 9.[11] In 2004, however, Mayo announced its intent to

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[11] Prometheus's test remains in Mayo's test catalog. *See* http://www.mayomedicallaboratories.com/test-catalog/Overview/91564 (last visited Oct. 25, 2011).

sell its own competing test called "Azathioprine Metabolites Profile, Blood." *See* Pet.App.6a; 2JA40; *see also* 1JA9-13 (recounting Mayo's business motive).

Mayo's test (like Prometheus's) is intended for "[p]hysicians who are treating patients," 1JA7; it measures the same metabolites as Prometheus's test; and it specifies similar metabolite levels for ensuring efficacy and avoiding toxicity. Pet.App.6a, 111a-12a; 2JA40. Indeed, Mayo developed its test using Prometheus's test as a model. *See* Dkt.146 at 67-69. One of the test developers explained that, because "Prometheus was the only other provider of this method," Mayo used Prometheus's test "[a]s a measure of accuracy" to "validat[e]" Mayo's method. *Id.* at 69; *see also id.* at 52 ("Prometheus is the only lab in the United States doing Azathioprine metabolite .... Why reinvent the wheel?"); Dkt.528 Morgan Decl. Ex. 17.

Mayo was poised to earn a 60% profit margin on this commercial test. 1JA28. When Prometheus brought the present suit, Mayo stayed its hand. Pet.App.6a; CA10905. But Mayo is anxious to "begin selling its competitive product." Appellees' Opp. to Mot. to Stay 4 (Fed. Cir. Aug. 11, 2008).

B. Procedural Background

1. *District Court Proceedings.* When Prometheus learned that Mayo Labs, Mayo's for-profit arm, intended to market a practically identical competing test, it filed this action for patent infringement. Pet.App.6a; CA10036-41. Prometheus alleged that Mayo Labs infringed "directly, contributorily, and by inducement of others, by making, using selling, importing and/or offering for sale methods ... covered by [the patents]." CA10037-38. Mayo Labs counterclaimed for declaratory relief of non-

infringement and of patent invalidity under 35 U.S.C. §§101, 102, 103, and 112. CA10045.

On cross-motions for summary judgment, the district court held that Mayo's test, as offered for sale, "literally infringes all elements of the patents-in-suit." Pet.App.115a. Mayo Labs had argued that it did not infringe because it specified a slightly different range of metabolites as the optimal therapeutic window. The district court, however, found that the term "about" as used in the claims' "wherein" clauses means plus-or-minus-15%, and concluded that Mayo's test infringed because Mayo's upper 6-TG threshold (450 pmol per $8x10^8$ red blood cells) was within 15% of Prometheus's upper level (400 pmol per $8x10^8$ red blood cells). Pet.App.113a-14a.[12] Mayo has not contested that construction.

Prometheus later amended its complaint to add Mayo Clinic, Mayo's non-profit arm. *See* 1JA14; Dkt. 110, 234. Prometheus alleged that Mayo Labs and Mayo Clinic infringed the asserted claims by, respectively, offering Mayo's test for sale and using Mayo's test, 2JA43, 58. Prometheus also alleged that Mayo Labs induced Mayo Clinic to infringe by performing the patented methods on patients of Mayo Clinic's employees, including Dr. Rokea el-Azhary. 2JA48, 53-54, 64-65, 70.[13]

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[12] The court did not need to address whether Mayo's 5700 upper 6-MMP threshold infringed Prometheus's 7000 level. Pet.App.113a n.16.

[13] Mayo's characterizations of Dr. el-Azhary's peripheral involvement in this matter are both irrelevant (because the district court has not addressed the issues) and highly misleading. *See* Pet. Br. 11-13, 25, 34, 44, 47, 56. It is undisputed that Dr. el-

The district court then granted Mayo's motion to invalidate Prometheus's claims for lack of patentable subject matter under 35 U.S.C. §101. Pet.App.83a. The court concluded that Prometheus's claims do not

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Azhary's patients were administered thiopurines for treatment of an autoimmune disease covered by the patented claims, and that Mayo measured the level of the indicated metabolites and provided a report of the metabolite measurements along with Prometheus's 6-TG correlation. *See* 2JA53-57; 1JA5-6, 20-22; Dkt.146 Ex.27. Mayo insists that Dr. el-Azhary did not believe that Prometheus's thiopurine metabolite correlations accurately describe the therapeutic range for the disease at issue. Pet. Br. 11-13, 34. But that is a disputed question of fact. One of Mayo's test developers conceded that, when Mayo reported the blood metabolite levels to Dr. el-Azhary, it noted "in the patient's interest" that the "therapeutic range" for 6-TG was between 235 and 400 in "an attempt to alert her that [some of] those values seemed abnormal according to literature values." 1JA5. If Mayo is correct that Dr. el-Azhary ignored or disbelieved Mayo's alert, Prometheus would agree that this particular allegation of induced infringement would fail (because Dr. el-Azhary would not have been "warned" by a comparison of the metabolite measurements to Prometheus's correlations).

Contrary to Mayo's assertion (at 13), moreover, Prometheus has never claimed that Dr. el-Azhary must stop her dermatological research until she purges her memory of the correlations. If she is using meaningfully different correlations to calibrate her patients' thiopurine treatments, she is not infringing the patents. If she is using Prometheus's correlations (and performing the other steps of the asserted claims) in patient treatment, Mayo can pay Prometheus for her tests as it has routinely for its other physicians since 1999.

Finally, Prometheus has never contended—and would never contend—that Dr. el-Azhary or Mayo would infringe the patents merely by publishing an article that says that Prometheus's correlations are inaccurate (or, for that matter, accurate). Mayo cites no evidence for its repeated insistence that Dr. el-Azhary (irrationally) did not "dare[]" publish an article for fear of infringing these patents. *See* Pet. Br. 13, 25, 47.

describe a "process" only after dissecting the claims into their constituent parts and disregarding the physical steps. The court held that the claims' first two steps (administering the thiopurine compound and determining the resulting metabolite concentrations) should be disregarded because they are mere "conventional" or "data-gathering" steps that are not independently novel. Pet.App.62a. Having limited its analysis to the third—"warning"—step, the court concluded that the patents improperly claim dominion over "the correlations themselves." Pet.App.62a-63a.[14] The court considered these correlations to be "natural phenomena" because they "result[] from innate metabolic activity in the human body," Pet.App.63a-71a, even though thiopurine metabolites indisputably do not occur naturally in the human body and are created only through human intervention. The court further concluded that the patents "'wholly pre-empt' use of the natural phenomenon such that the 'practical effect is [an improper] patent on the [phenomenon] itself.'" Pet.App.72a (quoting *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972)) (second alteration in original).

2. *Federal Circuit's First Decision.* The Federal Circuit reversed. Applying the machine-or-

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[14] The district court rejected Prometheus's argument that the third step requires "that the doctor (or any person) 'provide' a warning." Pet.App.63a. Under the district court's claim construction, by reference to the correlations "it is the metabolite levels themselves that 'warn' the doctor that an adjustment in dosage may be required." *Id.* Accordingly, a doctor who does not believe Prometheus's correlations are accurate is not "warned" within the meaning of these patents of a potential need to alter dosage—and thus does not infringe the claims. Prometheus has not challenged that ruling.

transformation test, the court held that Prometheus's methods "squarely fall within the realm of patentable subject matter because they 'transform an article into a different state or thing,' and this transformation is 'central to the purpose of the claimed process.'" Pet.App.40a (citation omitted). Specifically, it determined that the claims entail at least two integral transformations. First, "[w]hen administering a drug such as AZA or 6-MP, the human body *necessarily* undergoes a transformation" in response to the administration of these synthetic drugs. Pet.App.41a (emphasis added). Second, "[d]etermining the levels of 6-TG or 6-MMP in a subject necessarily involves a transformation," because "[s]ome form of manipulation, such as the high pressure liquid chromatography ... is necessary to extract the metabolites from a bodily sample." Pet.App.42a-43a. "'[A]t the end of the [determination] process, the human blood sample is no longer human blood; human tissue is no longer human tissue.'" Pet.App.43a (citation omitted).

The Federal Circuit concluded that these transformations cannot be disregarded as "mere[] data-gathering" or "'insignificant extra-solution activity'" appended to a bare recitation of the correlations, Pet.App.44a-45a (citation omitted), because it construed the claims as limited to the *patient treatment* context. *See, e.g.*, Pet.App.41a ("The invention's purpose to treat the human body is made clear in the specification and preambles of the asserted claims."). It explained that "the administering step provides thiopurine drugs *for the purpose of treating disease*, and the determining step measures the drugs' metabolite levels *for the purpose of assessing the drugs' dosage during the course of treatment.*"

Pet.App.44a (emphasis added). The transformations, therefore, are not peripheral or tacked-on, but "central to the claimed methods" and "'sufficiently definite to confine the patent monopoly within rather definite bounds.'" Pet.App.42a (citation omitted).

Further, the court held that the inclusion of a mental step—even as the final step—does not render an otherwise patentable process unpatentable. Pet.App.45a-47a. It explained that, "[a]lthough a physician is not required" in the "warning" step "to make any upward or downward adjustment in dosage," the process taken as a whole "provide[s] useful information for possible dosage adjustments to the method of treatment using thiopurine drugs for a particular subject." Pet.App.47a.

Although it believed the integral involvement of transformations was dispositive of the §101 inquiry, the Federal Circuit distinctly addressed, and rejected, the district court's finding that the claims impermissibly preempt all practical uses of a natural phenomenon. The court explained that "the claims do not preempt natural processes" but instead "utilize them in a series of specific steps ... comprising particular methods of treatment." Pet.App.48a. (citing *Diehr*, 450 U.S. at 187). As in *Diehr*, Prometheus's method patents "'seek only to foreclose from others the use of that [principle] in conjunction with all of the other steps in their claimed process.'" *Id.* (quoting *Diehr*, 450 U.S. at 187).

The Federal Circuit emphasized that "the only issue" it was addressing was "whether the claims meet the requirements of §101" and that the appeal did "not raise any questions about lack of novelty, obviousness, or overbreadth, since those are separate statutory

requirements for patentability under §§102, 103, and 112, respectively." Pet.App.39a.

3. *This Court's Initial Grant of Certiorari.* While Mayo's first certiorari petition was pending, this Court decided *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). The Court in *Bilski* rejected two proposed nonstatutory "categorical" limitations on §101 patentability. *Id.* at 3229. First, the Court held that the machine-or-transformation test is an important tool for determining patent eligibility, but that an invention may be patent-eligible even if it does not satisfy that test. *Id.* at 3227. Second, the Court held that business method patents are not *per se* unpatentable. *Id.* at 3228-29. Ultimately, however, the Court found that the particular business method claims at issue did not constitute statutory "processes" because, evaluated as a whole, they merely described the abstract idea of risk hedging and would "preempt" use of that broad concept "in all fields." *Id.* at 3229-31 (applying *Benson* and *Parker v. Flook*, 437 U.S. 584 (1978), as "limited" by *Diehr*).

The Court then vacated the Federal Circuit's first decision in this case and remanded for further consideration in light of *Bilski*. Pet.App.24a.

4. *Federal Circuit's Second Decision.* After supplemental briefing, the Federal Circuit (with two new panel members) again held Prometheus's methods patentable under §101. The court explained that, under *Bilski*, patent eligibility turns on whether Prometheus's claims "are drawn to a natural phenomenon, the patenting of which would entirely preempt its use as in *Benson* or *Flook*, or whether the claims are drawn only to a particular application of that

phenomenon as in *Diehr*." Pet.App.12a (citing *Bilski*, 130 S. Ct. at 3230).

The Federal Circuit cited *Bilski*'s reaffirmation that the machine-or-transformation test remains a "'useful and important clue'" to patentability, and once again found that Prometheus's patents satisfy the "transformation prong" of that test because the claimed methods transform an article into a "'different state or thing'" and the transformations are central to the treatment purpose of the claims. Pet.App.14a-16a (quoting *Bilski*, 130 S. Ct. at 3227). The court also reaffirmed that the patents do not impermissibly preempt a natural phenomenon by claiming particular applications of the recited thiopurine correlations. Pet.App.15a.

SUMMARY OF ARGUMENT

I. The judicially crafted principle that "natural phenomena" and "abstract ideas" are not eligible for patent protection under §101 reflects two distinct concerns. First, to be patent-eligible, a process must really be a *process*—a series of steps that involve physical action in the real world, as opposed to merely an idea or principle stated in the abstract. Second, that process must be described at a narrow and specific enough level of generality that it does not preempt abstract ideas or basic building blocks of science that go far beyond what the patentee actually invented: A process for using a telegraph is patentable; the basic idea that information might be transmitted at a distance by exploiting laws of electromagnetism is not.

A. Prometheus's patented methods describe concrete methods for improving treatment of seriously ill patients with specific synthetic drugs. These patents do not claim the "correlations" they employ in

the abstract, but as part of specific physical processes employing drugs and machines. The traditional machine-or-transformation test provides an important clue to patentability because it crisply distinguishes mere abstractions from processes that operate in the real world. As the Federal Circuit recognized, the patents-in-suit pass that test with flying colors and easily satisfy the requirements of §101.

Mayo attempts to avoid that conclusion in three ways, none of which has merit. First, Mayo invites this Court to discard the two initial steps (administering the thiopurines and determining the resulting metabolite levels) because they were "well known" in the art. But this Court rejected that "point-of-novelty" approach over 30 years ago in *Diehr* and again recently in *Bilski*. Second, Mayo argues that those same two initial steps should be disregarded because, according to Mayo, they are not "central" to the patents' purpose. Mayo does this only by ignoring the Federal Circuit's settled construction that the claims are limited to patient treatment (a question not presented here) and that those two steps are *essential* to that purpose. Third, Mayo invites this Court to invent, out of whole cloth, a categorical rule that processes ending with the provision of useful information cannot be patentable—even if preceding steps involve machines and physical transformations. That argument also is inconsistent with *Bilski*, and it would impose an arbitrary and (in the information age) absurd limitation on patentability.

B. The patents-in-suit do not preempt natural phenomena in any relevant sense. Their "correlations" concern certain properties attending certain uses of non-natural thiopurine compounds, which would not exist but for the handiwork of man. A patent system

that recognizes thiopurine compounds themselves as potentially patentable subject matter, allowing preemption of *all* uses of these compounds, cannot be concerned that a process patent may preempt *some* of their uses. The extent of any preemption, moreover, is exceedingly narrow. These patents do not claim the abstract idea of calibrating drug doses by measuring metabolites or all ways of calibrating thiopurines. The transformations, ties to statutory subject matter, and limitation to treatment ensure that these patents merely claim, and preempt, one particular way to improve the treatment of patients suffering from certain diseases. That is precisely the sort of monopoly the patent system is meant to convey, not one of the basic building blocks of nature with which this Court's preemption analysis is concerned.

C. Prometheus agrees with the United States that the Patent Act's express statutory criteria for patentability—under 35 U.S.C. §§102, 103, and 112—make expansive judicial lawmaking under §101, of the sort invited by Mayo's arguments, unnecessary. But the application of those provisions is not before the Court in this case, and presents difficult and fact-bound questions that the lower courts should address in the first instance on remand.

II. Mayo proposes to transform §101 into an invitation for *ad hoc*, case-by-case evaluation of whether granting a particular patent will promote or retard the progress of the useful arts. That would create an unadministrable morass for courts and patent examiners, doom any hope for consistent administration of the patent laws, and usurp *Congress's* authority to determine the appropriate scope of the patent laws.

III. Any change in the Court's §101 jurisprudence that permitted a ruling in Mayo's favor, on whatever grounds, would have drastic and unfortunate consequences. It would upend settled expectations by invalidating thousands of diagnostic and personalized treatment patents. And it would stifle investment and innovation in the nascent field of personalized medicine. Contrary to Mayo's understanding, government funding does not translate pure academic research into practical products that benefit patients, and doctors themselves cannot bring to bear the resources necessary to fuel innovation and commercialize inventions on a large scale.

Mayo's contention that patents like these hinder medical care is also unpersuasive. The United States is the world leader in biotechnology and personalized medicine, in part because investors have committed billions of dollars in capital in reliance on the prospect of patents like these. Thousands have been issued, including many to Mayo itself. Mayo's short-sighted view would exchange long-term innovation (including cost reductions) for ephemeral savings. In any event, Congress already considered Mayo's invitation to broadly restrict patent protection for medical diagnostic and treatment methods—and chose to adopt a limited personal immunity for doctors instead.

ARGUMENT

I. PROMETHEUS'S METHOD PATENTS FALL SQUARELY WITHIN §101

In the Patent Act of 1793, Congress authorized patent protection for "any new and useful art, machine, manufacture or composition of matter, or any new or useful improvement on [such statutory subject matter], not known or used before the application." Act of Feb.

21, 1793, ch. 11, §1, 1 Stat. 318, 319. That language remained relatively constant until 1952, when Congress reorganized and amended the statute. 35 U.S.C. §101 *et seq.*

The Patent Act of 1952 separated the basic subject matter definition (§101) from the novelty requirement (§102), and created a new "non-obviousness" provision (§103) that codified and provided a more definite standard for the necessary level of inventiveness. *See Diehr*, 450 U.S. at 189-91; *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1, 12-17 (1966); *see also* S. Rep. No. 82-1979, at 5-6 (1952). The 1952 legislation also replaced "art" with "process" and defined "process" to mean "process, art or method, ... includ[ing] a new use of a known process [or other statutory subject matter]." 35 U.S.C. §§100(b), 101 note. As enacted in 1952, §101 provides:

> Whoever invents or discovers *any* new and useful process, machine, manufacture, or composition of matter, or *any* new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. §101 (emphasis added).

"'In choosing such expansive terms ... modified by the comprehensive "any," Congress plainly contemplated that the patent laws would be given wide scope.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). As this Court has explained, §101 "is a 'dynamic provision designed to encompass new and unforeseen inventions,'" and courts are not free to "impose limitations ... that are inconsistent with the Act's text." *Id.* at 3227, 3231 (citation omitted).

Despite the Act's broad language, courts have long recognized an implicit limitation that patents cannot issue for "'laws of nature, natural phenomena, and abstract ideas.'" *Bilski*, 130 S. Ct. at 3238 (quoting *Diehr*, 450 U.S. at 185). But that limitation must be approached carefully, because "all inventions can be reduced to underlying principles of nature," *see Diehr*, 450 U.S. at 189 n.12, and §101 is intended as "only a threshold test" that "defines the subject matter that may be patented" and leaves the fact-intensive analyses of novelty, non-obviousness, and written description to the Act's substantive "'conditions and requirements.'" *Bilski*, 130 S. Ct. at 3225 (quoting §101).

Under this framework, distinguishing between a patentable "process" and an unpatentable "principle" has not always been a straightforward inquiry. *See Flook*, 437 U.S. at 589. But two related strands emerge consistently from this Court's jurisprudence. The first strand derives from the text, and focuses on whether a patent claims an incorporeal principle or instead an application of that principle within a physical process. *See* U.S. Br. 13 (exception "follows directly from the text" because principles and abstractions are not "processes"). The second strand is atextual but reflects a longstanding judicial appreciation that process patents cannot be crafted at such a high level of generality that they effectively preempt "basic tools of scientific and technological work," *Benson*, 409 U.S. at 67, and grant dominion over inventions that the patentee may never have envisioned, *O'Reilly v. Morse*, 56 U.S. 62, 112-14 (1854).

Prometheus's patents do not run afoul of either limitation: they claim concrete applications of principles

(not the principles themselves), and to the extent they can be said practically to preempt any scientific knowledge—*i.e.*, the relationship of particular metabolite levels to the efficacy or toxicity of the doses of particular synthetic drugs used to treat patients with particular diseases—it is only at the very granular level at which all patents, by design, preempt particular applications of scientific knowledge. Hence, as the United States recognizes, the patents in suit fall "squarely" within §101. U.S. Br. 32.

A. Prometheus's Patents Claim "Processes" Under §101

As this Court long ago explained, a "process" cognizable under the Patent Act is "a mode of treatment of certain materials to produce a given result"; it "requires that certain things should be done with certain substances, and in a certain order." *Cochrane v. Deener*, 94 U.S. 780, 788 (1877). On that understanding, a scientific fact or abstract idea—such as the Pythagorean Theorem, the law of gravity, the natural characteristics of bacteria, or "the basic concept of hedging"—is not a patentable process. *Bilski*, 130 S. Ct. at 3231. "A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented ...." *Le Roy v. Tatham*, 55 U.S. 156, 175 (1853).

Because all real-world processes must operate according to natural principles, concrete *applications* of such principles have always been understood to be patentable.[15] As one early court explained, "[t]he

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[15] *See, e.g.*, *Bilski*, 130 S. Ct. at 3230 ("'an *application* of a law of nature ... to a known structure or process'" is patentable (quoting *Diehr*, 450 U.S. at 187)); *Tilghman v. Proctor*, 102 U.S. 707, 724

instant that the principle, although discovered for the first time, is stated ... as the agent of[] producing a certain specified effect, it is no longer an abstract principle, it is then clothed with the language of practical application, and receives the impress of tangible direction to the actual business of human life." *Househill Coal & Iron Co. v. Neilson*, 1 Webs. Pat. Cas. 673, 684 (1843) (lower court op.). The process claims at issue here are patentable because they claim concrete applications of scientific principles, not principles in isolation.

Mayo urges this Court to ignore the initial physical steps of these treatment methods (either because they are not novel or because they are merely incidental) and reverse the decision below because the "warning" step *standing alone* would not be a §101 process. Alternatively Mayo contends that, regardless of the character of their initial steps, methods such as these must be categorically excluded from §101 because they end with an information-providing mental step. None of those arguments has merit.

1. These Patents Claim Concrete Applications

Prometheus's patents do not claim in the abstract the inventors' scientific discoveries about the relationship between 6-TG and 6-MMP metabolite levels and the efficacy or toxicity of a patient's dose, but instead claim processes which apply that

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(1881) ("[H]aving invented and practically exemplified a process for utilizing this [scientific] principle, ... he was entitled to a patent ...."); *Le Roy*, 55 U.S. at 175 ("The elements of the power exist; the invention is not in discovering them, but in applying them to useful objects.").

knowledge in a series of physical steps that enable physicians to improve patient treatment.

The traditional machine-or-transformation test confirms that Prometheus's patented methods do not claim principles in the abstract. In *Bilski*, this Court rejected the Federal Circuit's holding that a §101 process *necessarily requires* a machine or transformation. 130 S. Ct. at 3227. But every Justice in *Bilski* reaffirmed that the machine-or-transformation test remains "a useful and important clue" to patentability. *Id.*; *id.* at 3232 ("[T]he entire Court agrees[] that ... the machine-or-transformation test is reliable in most cases ...."') (Stevens, J., concurring in judgment); *id.* at 3258 ("'[T]ransformation and reduction of an article to a different state or thing is *the clue* to the patentability of a process claim that does not include particular machines.'") (Breyer, J., concurring in judgment) (citation omitted).

The Court has repeatedly looked to the machine-or-transformation test because a process necessarily constitutes a concrete application, and not merely an incorporeal fact or idea, if it transforms materials or works through other specific statutory subject matter, such as particular classes of machines or compositions of matter. Thus, for example, in *Diehr*, this Court affirmed the subject-matter eligibility of a patent on a process for curing synthetic rubber, which functioned by continuously updating a mathematical calculation of the time to cure, as a function of temperature and pressure, in order to determine when to open the mold. 450 U.S. at 177-78. Of course that mathematical function (the "Arrhenius equation") standing alone was an abstract scientific principle. But the Court

reaffirmed its appreciation that a process constitutes a patentable application rather than a mere abstract principle when it "perform[s] a function which the patent laws were designed to protect" such as "transforming or reducing an article to a different state or thing." *Id.* at 192; *see also, e.g.*, *Benson*, 409 U.S. at 70.

The same conclusion should obtain here. Prometheus's patents claim the application of scientific knowledge, and not that knowledge in isolation, because they describe processes for improved medical treatment that operate through a series of specific, concrete steps that collectively satisfy both prongs of the machine-or-transformation test.

First, the patent claims entail two fundamental transformations. As the Federal Circuit explained, when thiopurines are administered "the human body *necessarily* undergoes a transformation" that produces 6-TG and 6-MMP. Pet.App.17a. And the subsequent "[d]etermin[ation] [of] the levels of 6-TG or 6-MMP in a subject [also] necessarily involves a transformation"; "'at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue.'" Pet.App.18a. (citation omitted); *see* 1JA30-31. These transformations, moreover, are integral to the patents' core purpose of improving treatment of patients with the indicated autoimmune diseases. The administered thiopurines create within the body active metabolites that transform the patient's physiology to a healthier state and, when measured in transformed blood or tissue samples, the indicated metabolites provide a means to better calibrate subsequent doses.

Second, although the Federal Circuit found it unnecessary to reach the issue, the patents also satisfy the "machine" prong of the test. The "determining" step of each claim necessarily requires the use of machines to determine metabolite levels from human blood or tissue samples. Several dependent claims specifically require HPLC, a multi-step, machine-bound process. *See supra* at 7-8. The claimed processes also require and are inextricably tied to synthetic thiopurine drugs, which are a potentially patentable "composition of matter" under §101. This Court's precedents have discussed statutory subject matter ties in terms of "machines," but there is no reason for these purposes to discriminate among the classes of statutory subject matter. The Patent Act's definition of "process"—including "a new use of a known process, machine, manufacture, composition of matter, or material," 35 U.S.C. §100(b)—draws no such distinctions, and this Court has long understood that "where the result or effect is produced by chemical action, by the operation or application of some element or power of nature, or of one substance to another, such modes, methods, or operations are [equally] called processes" within the statutory subject matter, *Tilghman v. Proctor*, 102 U.S. 707, 722 (1881). A tie to a particular class of compositions of matter, no less than a tie to a particular class of machines, ensures that the claim is to a concrete application rather than an abstract principle.[16]

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[16] Indeed, the lines between the different classes of statutory subject matter are increasingly indistinct. Proteins, for example, frequently do work (such as self-replication, transport of intracellular materials, and catalysis of a chemical reaction) analogous to work done by machines.

The administration of thiopurines and measurement of thiopurine metabolites, in the course of treating patients with particular autoimmune conditions, distinguishes the concrete and valid process claims at issue here from an abstract (and unpatentable) claim to the naked idea that doctors generally may calibrate medicine based on metabolite measurements. Mayo has never disputed that, in principle, both of the process's first two steps (administering thiopurines and determining metabolite levels) *standing alone* would constitute patentable "process[es]" under §101. Those steps do not become abstract or any less a "process" when they are combined and followed by an additional step that uses an algorithm (comparing the measurements to the threshold levels stated in the "wherein" clauses) to generate information useful for patient treatment. Indeed, the statutory definition explicitly contemplates that a patentable "process" can be built on other patentable processes, because a new use of an old process is patentable. 35 U.S.C. §100(b).

2. Novelty And Inventiveness Have No Role In The Threshold §101 Analysis

Throughout this litigation, Mayo has argued that the initial "administering" and "determining" steps should be disregarded under §101 because they were already "well known" in the art—and that Prometheus's patented methods therefore must be analyzed as if they constituted *solely* the final warning step.[17] Consistent with that argument, Mayo has

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[17] *See, e.g.*, Br. for Appellees 2, 4-5, 23-24, 30, 33-36 (Fed. Cir. Mar. 30, 2009); Cert. Pet. i, 3-6, 12, 15, 18, 19, 22, 24, 28 (Oct. 22, 2009) (No. 09-490); Supp. Br. of Defendants-Appellees 3, 11-12

suggested that these treatment methods might be patentable if Prometheus had invented thiopurines or the processes for measuring metabolites. *See, e.g.*, Pet. Br. 24, 35-36; *accord* ARUP Br. 10. But §101 is not about who invented what, or when. The internal combustion engine is still a "machine" and the method in *Diehr* is still a "process" under §101 today even though neither is novel anymore.

Mayo's mode of analysis is precisely the old "point-of-novelty" approach to §101 that this Court briefly embraced in *Flook*[18] but then unequivocally rejected in *Diehr* as an improper conflation of patentable subject matter with novelty issues that are properly treated under §102. *Diehr* stressed (and *Bilski* reiterated) that courts must consider the invention "as a whole" under §101 rather than "dissect[ing]" and discarding the old elements. 450 U.S. at 188; *see Bilski*, 130 S. Ct. at 3230. As the United States explains, *Diehr* superseded *Flook* and "subsequently clarified" that for §101 purposes a process claim must be considered as a whole, including both its old and its new elements. U.S. Br. 16-17; *see also Bilski*, 130 S. Ct. at 3230 (*Diehr* "limit[ed]" prior case law).

This Court could not have stated that point more clearly than when it said, without qualification, that considerations of the novelty or nonobviousness "of any element or steps in a process, or even of the process

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(Fed. Cir. Oct. 1, 2010); Pet. i, 3, 5 & n.2, 15, 24, 26, 30 (Mar. 17, 2011) (No. 10-1150); Pet. Br. 5, 19, 24, 35-37.

[18] The Court in *Flook*, 437 U.S. at 591, relied on dicta from *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948), which was decided before the 1952 Act moved the statute's novelty condition to §102 and codified the judicial concern for inventiveness as non-obviousness in §103.

itself," are of "no relevance in determining whether the subject matter of a claim falls within the §101 categories of possibly patentable subject matter." *Diehr*, 450 U.S. at 188-89. The Court took pains to refute the specific argument Mayo now advances, explaining that "an *application* of a law of nature or mathematical formula to a *known ... process*" is patentable. *See id.* at 187 (second emphasis added). Indeed, *Diehr* declared that a series of steps is a patentable process even if "all the constituents of the combination were well known and in common use." *Id.* at 188.

In reaching those conclusions, this Court adhered to the plain language of the statute. Section 100(b)'s definition of "process" expressly includes "a new use of a known process, machine, manufacture, composition of matter, or material." 35 U.S.C. §100(b). That language was intended to dispel any prior doubts[19] about whether "new uses" of old processes are patentable. *See, e.g.*, 35 U.S.C. §101 note; S. Rep. No. 82-1979, at 5. It equally dispels Mayo's argument. If "process" embraces new uses of old statutory subject matter, it unquestionably embraces a new treatment protocol that combines well-known and independently patent-eligible processes (administration of thiopurines and measurement of resulting metabolites) with useful knowledge about patient physiology.

Mayo and its *amici* also urge the Court to peek at novelty and non-obviousness during the §101 inquiry by assuming that any natural principle expressed in a

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[19] *See, e.g., In Re Thuau*, 135 F.2d 344, 346 (C.C.P.A. 1943) ("[A] new use of an old thing or an old process, quite unchanged, can under no circumstances be patentable ....").

claim is old in the art and requiring a demonstration that the principle has been used in an "inventive" manner. *See, e.g.*, Pet. Br. 35-37; Law Professors Br. 2-4; ACMG Br. 18-33; ARUP Br. 19; *cf.* Pet. Br. 19 (steps that are "well known" and "long prevalent" "do nothing to narrow the scope of preemption of the biological phenomenon"). This is merely the point-of-novelty approach in new garb. It conflicts just as squarely with *Diehr*'s emphatic holding that novelty and non-obviousness are irrelevant to the §101 analysis. 450 U.S. at 191. And it blatantly ignores the fact that, in the 1952 Act, Congress moved the statute's novelty condition to §102 and created a new §103 to codify with "uniformity and definiteness" the judicial requirement of inventiveness that had previously been enforced under §101's predecessors. *See Graham*, 383 U.S. at 15; S. Rep. No. 82-1979, at 5-6.

There is no reason for this Court to reconsider its holding in *Diehr*, which it so recently reaffirmed in *Bilski*. The Professors protest (at 29-33) that the Court must import "inventiveness" back into §101 because, otherwise, the claims here might survive under §§102 and 103. But arguing backwards from a desired outcome is hardly persuasive. The Professors offer no coherent statutory justification for introducing into §101 a quick-and-dirty "inventive creativity" requirement that differs substantively from the express standards of §§102 and 103. Ultimately, the Professors rest on their belief that considering inventiveness as a threshold inquiry would send a clearer "signal[]" than analyzing the issue under the Act's express novelty and non-obviousness standards. That is dubious, but in any event an issue for Congress not the courts.

3. The Claims' Initial Steps Cannot Be Disregarded As Incidental

Mayo presumes throughout its brief that Prometheus's patented methods are not limited to actual medical treatment and instead would make an infringer of anyone who even thinks about the indicated correlations in the abstract. *See, e.g.*, Pet. Br. 2, 6, 7, 17-18. Mayo attempts in that way to recast the claims' administering and determining steps as mere incidental, extra-solution, data-gathering activity that "have no limiting effect on the claimed monopoly." Pet. Br. 20, 39. But the straw man that Mayo attacks bears *no* resemblance to the case that is actually before this Court.

Two different panels of the Federal Circuit analyzed the patents-in-suit as a whole and construed the claims as being limited to patient treatment. Pet.App.16a-17a, 40a-41a. Mayo did not ask this Court to review the Federal Circuit's claim construction. And this Court surely would not have taken the case for that purpose. The Federal Circuit's construction of these claims should, therefore, be respected as law of the case.

In any event, the Federal Circuit's claim construction is plainly correct. The first process step—"administ[ration] of [a thiopurine compound] to a subject having [an autoimmune disease]," *e.g.*, 2JA16—by definition only happens in the context of patient treatment because thiopurines are highly toxic and would not otherwise be used. *See, e.g.*, CA12705. Similarly, the "wherein" clauses—which require a warning of a potential therapeutic "need to increase the amount of said drug subsequently administered to said subject," *e.g.*, 2JA16—only make sense in the

context of medical treatment. The rest of the intrinsic record, moreover, including the claim preambles and specification, confirms that the claims are limited to methods of actual patient treatment, *see, e.g.*, 2JA7, 16-17—as the Federal Circuit found, Pet.App.16a-17a, 40a-41a.

Mayo thus wrongly asserts that the patents-in-suit might randomly ensnare doctors or researchers who do nothing more than inadvertently hear or think about the identified correlations between metabolite levels and drug efficacy or toxicity. *E.g.*, Pet. Br. 34, 37, 46-47. No one infringes these treatment patents merely by thinking about correlations or performing research outside of the treatment setting.[20] Infringement occurs only when thiopurines are administered to a patient suffering from an autoimmune disorder, blood or tissue samples are extracted, specified metabolites' levels are measured using sophisticated scientific instruments, and the doctor is warned (by a comparison of those measurements with the indicated correlations) of a possible need to adjust subsequent dosages for better treatment. As the Federal Circuit explained, "a physician who only evaluates the result of the claimed methods, without carrying out the administering and/or determining steps that are present in all the claims, cannot infringe." Pet.App.21a-22a. Mayo cannot render the initial physical steps of these

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[20] Mayo's (and its *amici*'s) invocation of the First Amendment is therefore inapposite. *See, e.g.*, Pet. Br. 46-47; ACLU Br. 16-23. And, in any event, no First Amendment concerns were properly raised or passed upon below, and they cannot be smuggled in via "constitutional doubt" because a decision affirming the patentability of these claims under §101 would not determine whether the claims are valid in other respects, *see infra* §I.C.

methods incidental by wishing away the Federal Circuit's construction of the claims.

4. Section 101 Does Not Categorically Exclude Processes That End By Providing Useful Information

Mayo argues that Prometheus's claims are invalid under §101 because they do not *require* an adjustment of dosage and instead end in a "mental step" that merely provides "useful information." Pet. Br. 18-19, 22-24, 33-34. That argument has no basis in the statute, precedent, or logic.

Mayo's proposed categorical limitation is untethered to anything in the Patent Act's language or history, and ignores *Bilski*'s recent, emphatic rejection of judicially created, bright-line exclusions. 130 S. Ct. at 3229. As the Federal Circuit explained, "the addition of the mental steps to the claimed methods ... does not remove the prior two steps from that realm." Pet.App.21a. In *Diehr*, this Court similarly affirmed the patentability of process claims for curing rubber that used a mathematical equation (that could be solved mentally) to provide information about when to open a rubber mold. *See* 450 U.S. at 179 n.5. For §101 purposes, it cannot make any difference whether a patent uses an information-providing step as those claims did, in the *middle* of the process, or, as these claims do, at the *end* of the process. In either event, the patentee might face challenges proving that element of its infringement claim (*i.e.*, showing that the alleged infringer actually *performed* the mental step), but that is no reason to reject the patent-eligibility of such methods under §101.

Mayo's insistence that these patents should end with a physical step requiring the doctor to increase or decrease the next thiopurine dose in response to the information generated also makes no practical sense. As Mayo concedes, "[c]ase-by-case judgment" is "needed because patient-to-patient variability cannot be removed entirely even by observing metabolite levels." Pet. Br. 3. How a doctor incorporates information respecting these metabolite levels into particular treatment decisions may be affected by a host of other variables (*e.g.*, the severity of the autoimmune condition, the patient's general health, other medications, lifestyle choices, and risk tolerance). Mayo's categorical rule that all claims must end with an action step would just multiply byzantine claim drafting. A patentee would be required to attempt to set out and claim all of the manifold branches of possible therapeutic decision trees just in order to ensure that each process ends with an action step. That exercise is wasteful and unnecessary. This Court has routinely recognized that patents can properly leave ample room for "the judgment of the operator." *Mowry v. Whitney*, 81 U.S. 620, 645-46 (1872); *see also Minerals Separation, Ltd. v. Hyde*, 242 U.S. 261, 270-71 (1916). And that recognition is particularly apt here, as modern medicine is far too individualized for the rigid patent drafting requirement that Mayo advocates to be practical or desirable.

Nor would it make sense more generally, in today's information age, for this Court to rule under §101 that a process ending with a step that produces useful information is less patentable than a process that produces soap, rubber, or flour. The categorical prohibition that Mayo advocates would have precisely

the sorts of "wide-ranging and unforeseen impacts" that concerned this Court in *Bilski*, 130 S. Ct. at 3229-30. PTO has issued thousands of patents on medical and other methods that "end" precisely this way and the courts have long recognized their validity. *See infra* §III. And patents on information-producing methods are hardly limited to the medical context. PTO has issued innumerable similar patents in other fields, for uses ranging from sensing and diagnosing aircraft turbine engine conditions, to modeling the spread and containment of an oil spill, to "detecting airborne contaminants in real-time." U.S. Pat. Nos. 5,018,069, 7,136,793, 7,287,929; *see also, e.g.*, U.S. Pat. Nos. 5,633,173 (method for detecting defects in a semiconductor wafer), 6,313,640 ("method for diagnosing and measuring partial discharge on-line in a power transmission system"), 7,310,062 ("method to detect GPS signal tampering"). Nothing in *Bilski* was intended to "create uncertainty as to the patentability of ... advanced diagnostic medicine techniques," 130 S. Ct. at 3227 (Kennedy, J., plurality opinion), let alone all processes providing valuable information. Mayo's approach would do just that.

B. Prometheus's Patents Do Not Preempt All Practical Use Of Any Relevant Principle

Prometheus's claims do not inappropriately preempt all practical uses of natural phenomena, laws of nature or abstract ideas.

As the Federal Circuit emphasized, this aspect of the Court's §101 jurisprudence must be approached with care. Almost *any* patent will preempt all practical uses of a "natural principle" or "abstract idea" if the principles or ideas are described with great specificity.

All real-world processes operate according to natural laws, and "preempting" others from exploiting particular phenomena in particular ways is, after all, the point of a patent.

As the United States recognizes (at 19, 24 n.5), this judicially created preemption exception to §101 has been applied only when patents would practically foreclose all uses of truly fundamental principles, in the abstract and across a broad range of potential endeavors and future applications, monopolizing future inventions the patentee may never have conceived. The seminal case is *O'Reilly v. Morse*, 56 U.S. 62 (1854), which approved Samuel Morse's patents on the telegraph (and use thereof) but disapproved a broader claim to "'the use of the motive power of the electric or galvanic current ... however developed for marking or printing intelligible characters, signs, or letters, at any distances.'" *Id.* at 112 (quoting patent). This Court presciently anticipated that "[f]or aught that we now know some future inventor, in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in the plaintiff's specification," and that Morse therefore "claims an exclusive right to use a manner and process which he has not described and indeed had not invented." *Id.* at 113.

In the same vein, in *Benson*, this Court was concerned that the claim to the use on a computer of a formula for binary-coded decimal to pure-binary conversion was "not limited to any particular art or technology, to any particular apparatus or machinery, or to any particular end use." 409 U.S. at 64. "[T]he 'process' claim [was] so abstract and sweeping as to

cover both known and unknown uses" of the formula, which could "vary from the operation of a train to verification of drivers' licenses to researching the law books for precedents and ... be performed through any existing machinery or future-devised machinery or without any apparatus." *Id.* at 68.

The Court voiced similar concerns in *Flook*. There the patent "d[id] not purport to explain" how to select the numerical constants (the weighting factor and the margin of safety) or the process variable (*e.g.*, temperature), how to monitor the process variables, how the chemical processes work, or how to set off or adjust an alarm. 437 U.S. at 586. Instead "[a]ll that it provide[d] [was] a formula for computing an updated alarm limit," which might be applied to any process that a person might choose to monitor. *Id.*

And, in *Bilski*, the Court rejected a patent on "[t]he concept of hedging [risk]" because it was "an unpatentable abstract idea, just like the algorithms at issue in *Benson* and *Flook*" and "[a]llowing petitioners to patent risk hedging would pre-empt use of this approach in all fields." 130 S. Ct. at 3231; *see also, e.g.*, *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989) (invalidating patent covering abstract concept of diagnosing "'any complex system, whether it be electrical, mechanical, chemical, or biological, or combinations thereof'") (quoting patent); *see generally* Mark A. Lemley et al., *Life After* Bilski, 63 Stan. L. Rev. 1315, 1332-37 (2011) (§101 prohibits overclaiming that would hinder future innovation) .

On the other hand, this Court has had no concern with claims that preempt more narrowly defined scientific facts or principles. In *Tilghman*, 102 U.S. at 709, for example, the Court found patentable a process

for producing "fat acids and glycerine from fatty bodies by the action of water at a high temperature and pressure." That patent wholly preempted the "natural phenomenon" that water applied at high temperature and pressure would have the stated effect on fatty bodies. But it did not preempt the broader natural principle that high temperature and pressure tend to break chemical bonds, and it did not preclude the use of other methods to separate fat acids and glycerine from fatty bodies, such as sulfuric-acid distillation or steam distillation. *Id.*

Similarly, the patent in *Neilson* wholly preempted the "natural phenomenon" that "heating the blast, in a receptacle, between the blowing apparatus and the furnace" would cause iron to smelt more rapidly in a furnace. *Id.* at 724 (discussing *Neilson v. Harford*, 151 Eng. Rep. 1266 (Ex. 1841)). The classic Goodyear vulcanization patent wholly preempted the "natural phenomenon" that "subjecting [India rubber] to a high degree of heat when mixed with sulphur and a mineral salt" would make it more durable and useful. *Id.* at 722. And the patent at issue in *Diehr* wholly preempted the "natural phenomena" that the Arrhenius equation, continually applied, predicts the optimal time for opening a rubber mold. But none of those preempted the broader phenomenon that matter changes phase with temperature or prevented achievement of the same results (smelting iron or curing rubber) through other means. *See also Telephone Cases*, 126 U.S. 1, 532-35 (1888) (upholding patent on method for using electricity in a certain way to transmit voice at a distance); *O'Reilly*, 56 U.S. at 112 (upholding patent on method for using electricity in a certain way to transmit characters at a distance).

Prometheus's claims likewise do not preempt a natural phenomenon in any relevant (and prohibited) way. The "natural" correlations purportedly being preempted are, in fact, wholly *non*-natural. And those non-natural correlations are only being claimed in a narrow application.

1. Prometheus's Patents Do Not Recite Natural Phenomena

Mayo argues that Prometheus's patents, in reciting certain metabolite levels correlating to warnings for future treatment purposes, preempt all practical uses of the correlations. But to the extent the patents preempt most practical uses of those correlations, they do not preempt "natural phenomena" in any meaningful sense.

This Court's cases applying the "natural phenomena" exclusion from patentability have distinguished between phenomena that exist unchanged in their natural state (which may not be claimed) and those that would not exist but for the intervention of man (which may be claimed). In *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948), for example, in holding the composition patent invalid, the Court emphasized that the combined bacteria "perform in their natural way," that the "combination does not improve in any way their natural functioning," and that "[t]hey serve the ends nature originally provided and act quite independently of any effort of the patentee." In *Chakrabarty*, in contrast, the Court held that a "nonnaturally occurring" bacterium could be patented because it had "markedly different characteristics from any found in nature," unlike, for example, "a new mineral discovered in the earth or a new plant found in the wild." 447 U.S.

at 309-10. The altered bacteria in *Chakrabarty* were of course no less governed by natural laws than the unaltered bacteria in *Funk Bros.* But from a patentability perspective, the Court explained the crucial distinction is "between products of nature ... and human-made invention." *Id.* at 313.

Although *Funk Bros.* and *Chakrabarty* were not "process" cases, the distinction that drove their holdings applies *a fortiori* in the process context. If the initial patent on a man-made invention can lawfully preempt the manufacture and all uses of that invention, the law cannot be concerned with a process patent that preempts less than that. In this way, an integral tie to statutory subject matter will ensure that a patent does not preempt a "natural phenomenon" in any objectionable sense. Combustion inside an automobile engine is surely mediated by natural laws, but both the engine itself and an improved method for tuning the engine are nonetheless patentable.

That principle is sufficient to reject Mayo's preemption arguments. The claimed processes here introduce a synthetic thiopurine compound into a patient's body, determine the levels of certain resulting metabolites (that would not exist but for the introduction of that synthetic compound), and then based on those levels warn the physician of a potential need to increase or decrease the next dose of the synthetic compound. None of these steps would occur but for the handiwork of man. *See* 1JA25-27. (Ironically, what Mayo considers the body's "natural" response is, in fact, an artificial *suppression* of the body's natural immune system.) The correlations discovered and utilized by the inventors are, for §101 purposes, entirely *unnatural*. As the United States

explains, the correlations "exist[] *because* of human ingenuity, not antecedent to it." U.S. Br. 20.

At bottom, the patents here simply utilize scientific principles discovered about certain applications of thiopurines in processes to optimize those applications. Because all applications of thiopurines could in theory be preempted by a composition of matter patent, principles governing certain applications are not basic building blocks of science with which preemption analysis is concerned.

2. These Claims Are Preemptive Only In The Narrow, And Permissible, Sense That All Inventions Are

Even if these phenomena were "natural," Prometheus's patents on specific methods of improving the treatment of autoimmune diseases with specific drugs are narrowly drawn and do not preempt abstract principles or ideas in a relevant sense. The transformations, ties to statutory subject matter, and limitation to patient treatment confine the scope of the claims sufficiently to ensure that no fundamental building blocks are removed from the public realm. These patents have no far-reaching designs on fundamental concepts like the diagnosis of abnormalities in a "complex system," *see In re Grams*, 888 F.2d at 836, or on basic principles of biochemistry or pharmacology that govern how drugs are transformed into metabolites. Nor do they seek to preempt the abstract notion that the efficacy or toxicity of any drug might be correlated with the levels of resulting metabolites produced by the body.

These patents do not affect the use of other drugs (such as steroids) to treat the indicated diseases or the

use of thiopurines to treat other diseases (such as breast cancer or leukemia). Indeed, the patents do not even foreclose other means of calibrating thiopurines for treatment of the covered (autoimmune) diseases. In addition to the traditional "start low, go slow" technique, doctors also calibrate doses of these drugs by determining, via genotype and phenotype, the efficiency with which each individual (via the TPMT enzyme) will convert the drugs into 6-TG and 6-MMP metabolites. *See, e.g.*, 2JA13, 16; Ernest G. Seidman, *Clinical Use and Practical Application of TPMT Enzyme and 6-Mercaptopurine Metabolite Monitoring in IBD*, 3 Rev. Gastroenterological Disorders S30, S31 (2003). And doctors and scientists of course remain free to develop new and better ways to treat these diseases and to calibrate the drugs at issue. Indeed, Mayo itself implicitly acknowledges as much, claiming that its 5700 level for 6-MMP is "widely used today." *See* Pet. Br. 8 n.3. Processes that use that correlation do not infringe the patents-in-suit because 5700 is not "about 7000," *See* Pet.App.113a-14a (interpreting "about" as +/- 15%). The narrowly drafted patents-in-suit will thus pose no substantial "obstruction[] to follow-on innovation." Lemley, 63 Stan. L. Rev. at 1330; *see id.* at 1344 (concluding that the claims at issue here are "not generative, nor will [they] unduly bar future inventors").

For all of Mayo's complaints about "patent monopolies that interfere with the work of scientists," Pet. Br. 41, and "countless researchers and innovators who are paralyzed," Pet. 19, Mayo has yet to identify any substantial activity that is preempted by Prometheus's patents, aside from Mayo's desire to copy and market a competing commercial test for the exact

same application. These patents do not even arguably preempt researchers' use of the indicated correlations outside of active patient treatment. Mayo's incessant references to Dr. el-Azhary are red herrings. Prometheus has never claimed that its patents cover pure research. Dr. el-Azhary is peripherally involved in this case only because Mayo Labs, a for-profit commercial laboratory, induced Mayo Clinic to infringe by urging its employees—such as Dr. el-Azhary—to use Mayo's infringing test in lieu of Prometheus' product. If Dr. el-Azhary was not treating patients, there was no infringement. If she truly did not consider Prometheus's correlations when making treatment decisions for her patients (although there is evidence to the contrary) then there was also no infringement. *See supra* at 11 n.13. And Mayo's repeated assertion that Prometheus's patents prevented Dr. el-Azhary from publishing findings disputing Prometheus' correlations is fanciful. *Id.*

On their face, Prometheus's claims to particularized medical treatment methods look nothing like the abstractions rejected in *O'Reilly*, 56 U.S. at 112 (claiming all uses of electricity to write at a distance, "'however developed'" (quoting patent)); or *Benson*, 409 U.S. at 68 (where the uses of the mathematical algorithm could "vary from the operation of a train to verification of drivers' licenses to researching the law books for precedents"); or *Flook*, 437 U.S. at 586 (where there were a "broad range of potential uses of the method" because "[a]ll that it provides is a formula"); or *Bilski*, 130 S. Ct. at 3231 (where the method claimed "the basic concept of hedging [risk]"). In those cases, this Court was legitimately concerned that the abstract nature of the claims would allow the

patentees to preempt innovations they never conceived of. Not so here.

The claims in this case are also drawn far more narrowly than the diagnostic method that the dissenters found objectionable in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124, 125-39 (2006) ("*LabCorp*") (Breyer, J., dissenting from dismissal of writ). Unlike Prometheus's claims, the claim in *LabCorp* was not limited to improving a specific *medical treatment*; instead it recited a "method for detecting" a vitamin deficiency in any warm-blooded animal that could be used for any purpose, including pure research. Unlike Prometheus's claims, moreover, the claim in *LabCorp* did not recite specific trigger levels; instead it merely taught that "elevated" total homocysteine levels correlates to a particular vitamin deficiency. *Id.* at 129. And unlike Prometheus's claims, the claim in *LabCorp* did not involve synthetic drugs and non-naturally occurring correlations; instead, it was based on a "natural relationship between homocysteine and vitamin deficiency" that exists without any human intervention. *Id.*

This case is instead like *Diehr*, where this Court held that the patentee's rubber curing processes did not "seek to pre-empt the use of [a well-known mathematical] equation" but sought "only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." 450 U.S. at 187. Prometheus likewise claims "a series of steps comprising particular methods of treatment." Pet.App.15a. And, as in *Diehr*, the addition and application of a principle ("natural" or not) to an otherwise patentable series of method steps, does not

(and *cannot*) render the resulting process *un*patentable.

C. Sections 102 and 103 Must Await Remand

The patents–in-suit might well eventually be analyzed under §§102 and 103 (and §112). But the application of those provisions to this case now would be premature. It was not addressed by the lower courts; it is not within the question presented, *see* S. Ct. R. 14.1(a); and the factual record of how those provisions might apply to this case has not yet been developed. As the United States recognizes, "[t]his Court should not resolve such questions in the first instance." U.S. Br. 27. Resolution of those issues, to the extent preserved, must await remand. *Id.* at 11-12.

Nonetheless, the United States suggests that this "Court's analysis of the Section 101 question ... should be informed by" the government's "understanding of the way in which other Patent Act provisions address petitioners' central objection to the '623 and '302 patents." *Id.* at 27. The United States then urges this Court to share its view that, because they "differ[] from the prior art only with respect to the mental inference a doctor may draw after the 'administering' and 'determining' steps have been completed," the claims at issue are inherently anticipated by prior art—making them either non-novel or obvious. *Id.* at 26-31. With due respect to the government's preliminary thoughts, the complexity of the issues it raises argues powerfully against this Court making any determination about the appropriate analysis of these claims under §§102 or 103 without the benefit of factual development and full briefing. As Professors Burk and Lemley have explained, inherency is "perhaps the most

elusive doctrine in all of patent law." Dan L. Burk & Mark A. Lemley, *Inherency*, 47 Wm. & Mary L. Rev. 371, 373 (2005). Indeed, Mayo's law professor *amici* acknowledge (at 31) that claims like those at issue may satisfy §§102 and 103.

To weigh in prematurely, even in dicta, would risk unforeseen consequences and untoward damage to countless diagnostic patents and computer-aided inventions that end with algorithms permitting users to interpret information. For example, in *Arrhythmia Research Technology, Inc. v. Corazonix Corp.*, 958 F.2d 1053 (Fed. Cir. 1992), the Federal Circuit approved a method patent for processing electrocardiograph signals (which were ubiquitous in the art) through a complex mathematical algorithm and then "comparing" the resulting value with a level that had previously been determined to gauge the patient's risk of ventricular tachycardia. 958 F.2d at 1055; *see also In re Abele*, 684 F.2d 902 (C.C.P.A. 1982) (affirming patent-eligibility of process using algorithm to improve graphic images in CAT scans). Under the government's view, all such information-generating processes in the medical and computer fields would apparently fail under §§102 and 103. An issue of this magnitude must be approached with deliberation and due care.

Contrary to the United States's suggestion, moreover, Prometheus's patented methods do not fit neatly into the cited inherency precedents. Under those precedents, if the prior art cannot be practiced without also *inevitably* performing the purportedly new claim limitations, the new process is inherently anticipated by the prior art. *See, e.g., Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268-69 (Fed. Cir.

1991). Likewise, merely recognizing a new benefit already inherently conferred by an old process does nothing to transform the existing process. *See, e.g.*, *King Pharms., Inc. v. Eon Labs, Inc.*, 616 F.3d 1267, 1277-79 (Fed. Cir. 2010). But at the same time it is well established that others' "incomplete and imperfect experiments" will not render a later successful invention anticipated. *Am. Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566, 595 (1874); *accord Telephone Cases*, 126 U.S. at 545 ("The difference between the two is just the difference between failure and success.").

On remand, Prometheus believes Mayo will be unable to demonstrate that the patented methods here involve steps and limitations that were *necessarily and inevitably* performed in the prior art (or are otherwise invalid under §§102 or 103). Although thiopurine drugs were administered for autoimmune diseases and researchers knew how to measure 6-TG and 6-MMP concentrations, there is no evidence that physicians treating autoimmune diseases measured thiopurine metabolites for clinical purposes before Prometheus's patents. *See supra* at 5-6. Prometheus, therefore, did not "'merely discover[] and claim[] a new benefit of an old process.'" *King Pharma*, 616 F.3d at 1275 (citation omitted). It identified the information necessary to make the combined steps clinically useful. *See* Burk & Lemley, 47 Wm. & Mary L. Rev. at 374 ("[I]f the public doesn't [already] benefit from the invention, there is no inherency.").

Prometheus will litigate all of these issues fully, with the benefit of briefing and factual development, if and when they are properly raised below. But they are not currently before this Court.

II. SECTION 101 DOES NOT INVITE A FREEWHEELING EXAMINATION OF THE LIKELY VALUE OF EACH PATENT

Mayo insists that, to decide the threshold question whether "'certain subject matter'" falls within §101, the federal courts (and, presumably, thousands of individual PTO examiners) should in each case "'ask whether granting [the] patents ... in fact will promote [scientific] progress' or instead 'hinder competition that can effectively spur innovation.'" Pet. Br. 43 (quoting a 2003 FTC report). This Court should reject that proposition. As the Court has recognized, "the decision as to what will accomplish the greatest good for the inventor, the Government and the public rests with the Congress," *United States v. Dubilier Condenser Corp.*, 289 U.S. 178, 198-99 (1933), and "courts should not read into the patent laws limitations and conditions which the legislature has not expressed," *Diehr*, 450 U.S. at 182 (internal quotation marks and citations omitted).

When this Court explained in *Diehr* that subject matter eligibility must be confined to the kinds of inventions that "the patent laws were designed to protect," *id.* at 193, that was not, as Mayo would have it (Pet. Br. 46), an invitation for *ad hoc* judicial policymaking. As Chief Judge Rader recently explained, parties like Mayo who advocate a sweeping role for §101 threaten to turn the Patent Act's limited threshold inquiry into a new "substantive due process" of patent law, with all of the practical and legal problems that would entail. *Classen Immunotherapies, Inc. v. Biogen IDEC*, — F.3d —, Nos. 2006-1634, 2006-1649, 2011 WL 3835409, at *15 (Fed. Cir. Aug. 31, 2011) (additional views). Adding such amorphous and labor-intensive inquiries would

"exacerbate PTO's already formidable task of ensuring that more than 6500 patent examiners apply Section 101 in a predictable and consistent fashion," U.S. Br. 32, and burden district courts and litigants with indeterminate policy questions that the judiciary is not equipped to resolve. "Clear definitions of the classes of subject matter in Section 101 provide critical guidance to the public, inventors, and the PTO regarding the boundaries of the patent laws." U.S. *Bilski* Br. 44 (Sept. 25, 2009). A system that asks thousands of examiners and hundreds of courts to decide for themselves, in the abstract, whether patent protection for an invention would promote or retard scientific progress would impose staggering costs on the patent system, eliminate predictability, and diminish incentives for innovation.

Judge Hand's observation a half-century ago is no less true today: "It is not for [the courts] to decide what 'discoveries' shall 'promote the progress of science and the useful arts' sufficiently to grant any 'exclusive right' of inventors." *Reiner v. I. Leon Co.*, 285 F.2d 501, 503 (2d Cir. 1960).

III. A RULING FOR MAYO WOULD DISRUPT SETTLED EXPECTATIONS AND HINDER INNOVATION

Contrary to Mayo's insistence (at 45-48) that it is merely seeking to enforce existing limits on subject-matter patentability, a ruling for Mayo, whatever the rationale, would mark a significant change in the law that would dramatically alter the status quo and upset settled expectations. The impact, moreover, would be widespread because essential features of Prometheus's methods—the application of scientific knowledge to identified and measured biomarkers to produce

information useful for clinical diagnosis and treatment—describe the core of personalized medicine and underlie thousands of existing patents in the field of personalized medicine.

A ruling for Mayo would eviscerate existing patents for a host of important diagnostic and treatment processes, ranging from a method for "determining increased risk of developing type II diabetes," to a method of predicting T-cell lymphoma patients' response to treatment, to a method for "test[ing] for West Nile virus." U.S. Pat. Nos. 7,635,559, 7,919,261, 7,384,785.[21] A diverse range of institutions have obtained such patents. *See, e.g.*, U.S. Pat. Nos. 4,968,603 (Univ. of Cal.) (breast and ovarian cancer), 7,993,830 (Laboratory Corp. of America) (prostate cancer), 7,323,346 (Mass. Gen. Hosp. and Harvard Univ.) (gestational disorders), 6,316,197 (United States) (anthrax exposure). Indeed, Mayo itself has obtained numerous such patents, including for a "diagnostic method" to detect the presence of inflammatory bowel disorder, consisting of "obtaining a physiological sample" and "determining the level" of a certain protein, "wherein the level is correlated to the presence or absence of said inflammatory bowel

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[21] *See also, e.g.*, U.S. Pat. Nos. 7,897,400 ("[n]on-invasive rapid diagnostic test for M. Tuberculosis infection"), 7,811,774 (method for classifying a breast tumor and assessing the prognosis), 7,709,222 (methods for making colon cancer prognoses using biomarkers), 7,670,792 (method for early detection of ovarian cancer using biomarkers), 7,482,135 (method for detecting kidney disorder), 6,972,180 (method of using saliva to diagnose and monitor breast cancer), 7,232,661 ("diagnostic method for prenatal identification of an increased risk of preterm delivery of a pregnant woman without clinical symptoms of preterm labor"); CA12939-3013 (collecting numerous such patents).

disorder." U.S. Pat. No. 5,928,883, CA12940. And examiners and courts have long recognized them as patentable. *See, e.g.*, *Arrhythmia Research Tech.*, 958 F.2d at 1054; *In re Abele*, 684 F.2d at 903-04, 908 & n.9; *see also* John F. Duffy, *Rules and Standards on the Forefront of Patentability*, 51 Wm. & Mary L. Rev. 609, 634-37 (2009) (discussing rise and demise of common law rule against patenting medial methods).

The consequences of an adverse ruling would of course not be limited to upsetting expectations on existing patents. More destructively, even, it would diminish the patent-based incentives that have made the United States the world leader in this field and decrease funding for future research and development. The principal medical advances of this century will likely arise from diagnoses of, and treatments optimized for, individual patients on the basis of genetic or other testing, like those described in the patents-in-suit or processes that identify biomarkers that make a patient likely to benefit (or not) from a uniquely targeted treatment. Such personalized medicine holds great promise for both enhancing patient care and reducing costs by permitting physicians to diagnose diseases earlier and more accurately, select the most effective treatment for a given patient, avoid unnecessary and costly treatments that are unlikely to work, and reduce adverse reactions. *See, e.g.*, Mara G. Aspinall & Richard G. Hamermesh, *Realizing the Promise of Personalized Medicine*, 85 Harv. Bus. Rev. 108, 109-11 (2007); Frances Toneguzzo, *Impact of Gene Patents on the Development of Molecular Diagnostics*, 5 Expert Op. Med. Diag. 273, 273 (2011); Personalized Medicine Coalition, *The Case For Personalized Medicine* 4-7

(2009) ("*Personalized Medicine*"); Roche Br. 2-3, 14. Personalized medicine also facilitates a shift to preventative care, which is typically less invasive and less expensive. *See Personalized Medicine* at 4.

The savings in health care costs from biomarker-related information that allows physicians immediately to identify optimal treatment and avoid adverse events are considerable—in some cases millions or billions from a single diagnostic regime. *See, e.g.*, *Personalized Medicine* at 7; PriceWaterhouseCoopers, *The New Science of Personalized Medicine: Translating the Promise Into Practice* 17 (Oct. 2009). For example, a genetic test to determine the proper dosage of a blood thinner could save $1.1 billion annually. Andrew McWilliam et al., AEI-Brookings Joint Center, *Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin*, Working Paper 06-23, at 12 (Nov. 2006). Doctors using Prometheus's patented methods are able to calibrate appropriate thiopurine dosage faster and at a lower cost than under the older "start low, go slow" approach. *See, e.g.*, Dubinsky, 100 Am. J. Gastroenterology at 2243 (finding that monitoring metabolites reduces costs by about 10% and time to effectiveness by about 14%).

But these innovations in personalized medicine are not free. Advancing the science and practice requires substantial investments—not only in the discovery of relevant biomarkers but also in completing the trials necessary to run the regulatory and third-party patient reimbursement gauntlets, and commercializing the basic science into products that actually benefit patients. *See* Roche Br. 4-16. Billions are invested annually in research and development of diagnostics and personalized medicine; indeed, bringing a single

diagnostic product to market can cost $10-$100 million. Roche Br. 3, 14-15 & n.6.

As Roche and Abbott Laboratories explain, strong patent protection is essential to incentivizing such private investment. *See* Roche Br. 4; *see also* Toneguzzo, 5 Expert Op. Med. Diag. at 274 ("industry has consistently confirmed that the protection that a patent affords is a key consideration for making an investment"); President's Council of Advisors on Sci. & Tech., *Priorities for Personalized Medicine* 21 (Sept. 2008) (patents are "essential" for the "large, high-risk R&D investments required to develop ... genomics-based molecular diagnostics"). Numerous *amici* in this and other cases— academics, universities, bar associations, trade organizations, and business interests—have recognized the same basic point.[22]

Conversely, weak or uncertain patent protection discourages capital investment. *See, e.g.*, Henry Grabowski et al., *The Market for Follow-On Biologics: How Will It Evolve?*, 25 Health Affairs 1291, 1300 (2006) ("[I]ncreased uncertainty and IP litigation in biotech also would have major negative-incentive effects on capital market decisions for developing private and public biotech firms with promising

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[22] *See, e.g.*, Br. of *Amici Curiae* Interested Patent Law Professors 13-16 (Fed. Cir. Jan. 18, 2009); Br. of *Amicus Curiae* Am. I.P. Law Ass'n 18-21 (Fed. Cir. Jan. 22, 2009); Br. of *Amici Curiae* Biotechnology Industry Org., Advanced Med. Tech. Ass'n, Wis. Alumni Research Found., and Regents of the Univ. of Cal. 4-5, *Bilski* (Aug. 6, 2009) ("BIO/University *Bilski* Br."); Br. *Amici Curiae* of Twenty Law and Business Professors 23, *Bilski* (Aug. 6, 2009); Br. of *Amici Curiae* Rosetta Genomics and George Mason University 9, *Ass'n for Molecular Pathology v. U.S. PTO*, No. 2010-1406 (Fed. Cir. Oct. 29, 2010).

pipelines."); Roche Br. 13-19; *see also* Federalist No. 62 ("What farmer or manufacturer will lay himself out for the encouragement given to any particular cultivation or establishment when he can have no assurance that his preparatory labors and advances will not render him a victim to an inconstant government?"). Invalidating the patents-in-suit and, by extension, countless others like them, would effect a "sea change" that creates "immeasurable uncertainty" and, "[w]ithout the confidence that investment-backed expectations can be realized, innovation will be retarded." Lawrence M. Sung, *Medical Alert: Alarming Challenges Facing Medical Technology Innovation*, 6 J. Bus. & Tech. L. 35, 58 (2011).

Mayo and its *amici* insist that federal government funding of basic research would fill the breach and provide the necessary dollars to incentivize innovation in personalized medicine. *See, e.g.*, Pet. Br. 51; Law Professors Br. 37. But even if the government were able to replace with public moneys all of the funds that are currently provided to universities and private companies through patent licensing fees, and even if government bureaucracies were as well-equipped as private actors to target funds to the most promising and valuable technologies, funding basic research alone would not provide the resources and incentives necessary to complete the full innovation life-cycle and "convert inventions that might otherwise exist only on paper into commercially viable products that improve the health and quality of life of the public." Roche Br. 13-14; *see also* BIO/University *Bilski* Br. 3-4. And the suggestion that innovation will nonetheless continue apace because doctors will perform the necessary research and development on their own, out of a sense

of duty or professional curiosity (Pet. Br. 44, 50-51), is shockingly naïve.

Mayo has not remotely demonstrated the wisdom of categorically eliminating patent incentives for private investment in this area. Although Mayo and its *amici* contend that patents like Prometheus's hinder innovation and degrade medical care, *see, e.g.*, Pet. Br. 40-45, 48-58; ACMG Br. 10-18, there is strong evidence to the contrary, *see* Roche Br. 19-25; Toneguzzo, 5 Expert Op. Med. Diag. at 274-75 (concluding that the real barriers are regulatory uncertainty and reimbursement by insurers); FTC, *Emerging Health Care Issues: Follow-up Biologic Drug Competition* 32 (2009).[23] Mayo's short-sighted approach seeks immediate savings in derogation of existing property interests and at the expense of great (and cost-effective) innovations over the long run.

Mayo's insistence (at 58) that enforcing patents like these "cannot be reconciled with the ethical duties of physicians" is even less persuasive. Prometheus's patents pose no unique threat to doctors' ethical obligations. Prometheus's test is widely available, and the fact that its price reflects a premium for innovation does not distinguish this invention from the thousands of patented drugs and medical instruments on which modern medicine also depends (and which physicians might also be duty-bound to employ). Despite its insistence that these patents are unethical, Mayo

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[23] Mayo's (and its *amici*'s) parade of horribles, such as a patent on weighing someone to determine their susceptibility to health risks, would as a practical matter be addressed under §§102 and 103. There is no reason to distort the threshold §101 inquiry based on such hypotheticals.

continues to this day to receive similar patents on methods of "monitoring" or "detecting" conditions in subjects, by "determining" and "detecting" characteristics in a sample, "wherein" the presence of those characteristics indicates a disease state. *See, e.g.* U.S. Pat. No. 7,998,670 (issued Aug. 16, 2011); U.S. Pat. No. 7,981,612 (issued July 19, 2011).

In any event, Congress has already considered these issues and, despite various invitations, has chosen not to restrict the patent-eligibility of medical processes. In 1995, Congress considered exempting certain medical methods from patent protection, but declined to do so. H.R. 1127, 104th Cong. (1995). And in 1996, Congress addressed the AMA's concerns about patent liability for doctors by providing a limited immunity from patent infringement liability for the performance of certain medical procedures—but Congress pointedly *did not* exempt such procedures from patent protection generally. 35 U.S.C. §287(c); *see* Pub. L. No. 104-208, §616, 110 Stat. 3009, 3009-67 (1996). Indeed, Congress declined to extend immunity to "the practice of a patented use of a composition of matter in violation of such patent," "the practice of a process in violation of a biotechnology patent," or the provision of "clinical laboratory services." 35 U.S.C. §287(c)(2)(A), (3). The legislative record demonstrates Congress's understanding that such methods are squarely within §101. *See Bilski*, 130 S. Ct. at 3228 (federal law "explicitly contemplates the existence" of business method patents); *J.E.M. Ag Supply, Inc., v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 145 (2001) (Congress "not only failed to pass legislation indicating that it disagrees with PTO's interpretation of §101, it has even recognized the availability of utility patents

for plants"); *accord* Duffy, 51 Wm. & Mary L. Rev. at 636-37 (noting that the new "statutory immunity ... accomplishes [the AMA's] specific goal without completely foreclosing the possibility that the granting of patents for medical treatment could be socially worthwhile").

As the United States emphasizes, "[m]ethods of practicing the medical arts have long been viewed as [patent-eligible]"—indeed, "PTO has granted more than 150,000" such patents—and "Congress has recognized that longstanding practice." U.S. Br. 15, 16. This Court should not accept Mayo's invitation to upend settled expectations and interject a destructive uncertainty in the patentability of medical methods, particularly where Congress has expressly chosen another path. Having failed to get what they wanted from Congress, Mayo and its *amici* approach this Court as if it were a legislature of last resort. The Court should politely but firmly turn them away.

CONCLUSION

The judgment of the court of appeals should be affirmed.

Respectfully submitted,

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35 U.S.C. § 100

§ 100. Definitions

When used in this title unless the context otherwise indicates—

* * *

(b) The term "process" means process, art or method, and includes a new use of a known process, machine, manufacture, composition of matter, or material.

* * *

35 U.S.C. § 101

§ 101. Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 287

§ 287. Limitation on damages and other remedies; marking and notice

* * *

(c)(1) With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b), the provisions of sections 281, 283, 284, and 285 shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity.

(2) For the purposes of this subsection:

(A) the term "medical activity" means the performance of a medical or surgical procedure on a body, but shall not include (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent, (ii) the practice of a patented use of a composition of matter in violation of such patent, or (iii) the practice of a process in violation of a biotechnology patent.

(B) the term "medical practitioner" means any natural person who is licensed by a State to provide the medical activity described in subsection (c)(1) or who is acting under the direction of such person in the performance of the medical activity.

(C) the term "related health care entity" shall mean an entity with which a medical practitioner has a professional affiliation under which the medical practitioner performs the medical activity, including but not limited to a nursing home, hospital, university, medical school, health maintenance organization, group medical practice, or a medical clinic.

(D) the term "professional affiliation" shall mean staff privileges, medical staff membership, employment or contractual relationship, partnership or ownership interest, academic appointment, or other affiliation under which a medical practitioner provides the medical activity on behalf of, or in association with, the health care entity.

(E) the term "body" shall mean a human body, organ or cadaver, or a nonhuman animal used in medical research or instruction directly relating to the treatment of humans.

(F) the term "patented use of a composition of matter" does not include a claim for a method of performing a medical or surgical procedure on a body that recites the use of a composition of matter where the use of that composition of matter does not directly contribute to achievement of the objective of the claimed method.

(G) the term "State" shall mean any state or territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.

(3) This subsection does not apply to the activities of any person, or employee or agent of such person (regardless of whether such person is a tax exempt organization under section 501(c) of the Internal Revenue Code), who is engaged in the commercial development, manufacture, sale, importation, or distribution of a machine, manufacture, or composition of matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office), where such activities are:

(A) directly related to the commercial development, manufacture, sale, importation, or

distribution of a machine, manufacture, or composition of matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office), and

(B) regulated under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Clinical Laboratories Improvement Act.

(4) This subsection shall not apply to any patent issued based on an application the earliest effective filing date of which is prior to September 30, 1996.

REPLY BRIEF

No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

REPLY BRIEF FOR PETITIONERS

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REPLY BRIEF FOR PETITIONERS

Prometheus's patents violate Section 101 because they wholly preempt an observed correlation between drug metabolites and patient health. Contrary to Prometheus's arguments, its patents are not narrow in scope. Unless physicians or researchers pay Prometheus they are precluded from making *any* use of the correlation between thiopurine metabolite levels and human health in connection with virtually all autoimmune diseases. This is so even though the patents describe no patient treatment, mandate no change in dosage, and do not prescribe any other steps to be taken by physicians. The patents therefore have the forbidden effect of preempting all uses of a physical phenomenon across a vast range of activity. Like the process patents held invalid in *Flook*, patents with such broad preemptive effect cannot be saved by adding the "conventional" activities of administering a "well known" drug and conducting a "long prevalent" blood test. 437 U.S. at 590, 594; *Bilski*, 130 S. Ct. at 3231.

Unlike the process of molding rubber in *Diehr*, Prometheus's process does not confine a natural law within specific steps, as Section 101 requires. Its patents foreclose physicians and researchers from even thinking about the natural correlation to produce *better* medical tests and *more accurate* metabolite ranges. Prometheus cannot foreclose medical advances that require application of improved medical judgment to the same natural phenomenon.

Section 101 is intended to weed out such invalid patents at an early stage. If it fails to do so, the federal courts and Patent Office will be flooded with

similar overreaching claims, with no means to filter out those that impermissibly prevent doctors and researchers from thinking about a patient's natural reaction to a drug or other therapy. Physicians will face a thicket of overlapping patents that cover every facet of medical practice. The threat of costly and time-consuming treble damages litigation that cannot be resolved without a trial will deter medical research and hurt patients—just as Prometheus's suit has stifled physician access to Mayo's improved test and to Dr. el-Azhary's research showing that Prometheus's metabolite ranges are harmful for dermatology patients.

Unless Section 101 bars the drafter's trick of embedding a natural phenomenon in token steps that do nothing to narrow the range of preemption, all the ill effects that Justice Breyer identified in *LabCorp* are certain to occur, as the American Medical Association and other medical groups and laboratories have explained. Medical costs will increase as physicians divert resources to patent searches, licensing, and litigation; and medical care will suffer as doctors are deterred from exercising medical judgment that might infringe broad and open-ended patents like Prometheus's. Nothing in the briefs of Prometheus or others who would gut Section 101, turning legally defective patent claims into occasions for a jury trial or forced license, explains why Congress would have intended this extraordinarily damaging result.

A. The Patent Office's Contention That Prometheus's Admittedly Invalid Patents Satisfy Section 101 Clashes With This Court's Precedents.

The government agrees (at 27-29) that Prometheus's "patents themselves make clear" that "the 'administering' and 'determining' steps of the disputed claims were part of the prior art" and that "the inventors' only asserted innovation" is a final mental step that "add[s] no patentable weight" to the claims. Accordingly, the government acknowledges (at 11) that Mayo's contention "that the claims are invalid appears to be correct."

The government's assertion that Prometheus's patents should be invalidated under the Section 102 and 103 "novelty" and "non-obviousness" standards rather than under Section 101's patent-eligibility standard is inconsistent with this Court's precedents. It would guarantee that patents on natural phenomena—rather than being invalidated at the Section 101 threshold with the least chill on innovation—instead spawn complex factual inquiries that often could not be resolved short of trial. And it so undermines the effective provision of health care that it cannot conceivably be what Congress intended.

1. The Patent Office recognizes that a patent on a natural "correlation itself" would be ineligible under Section 101. Br. 23. But it contends that adding conventional data-gathering steps like blood testing that have been used routinely throughout the medical profession is enough to create a patent-eligible "process." Br. 13-17. That toothless standard would make Section 101 meaningless as a constraint on monopolization of natural phenomena, for as

Justice Breyer observed in *LabCorp*, any natural phenomenon can be dressed up with "a series of steps." The important question is "what those steps embody." 548 U.S. at 137-138. Here, as in *LabCorp*, the steps are just "an instruction to read some numbers in light of medical knowledge." *Ibid.* Prometheus's own amici concede that its patents cannot survive under the standard stated by Justice Breyer, and not rejected by any Justice, in *LabCorp*. See Myriad Br. 22, 26; Novartis Br. 5, 7, 29.

Because Prometheus's claims are nothing but "prior art" plus a step of thinking about numbers that "add[s] no patentable weight" (U.S. Br. 28-29), they embody nothing innovative or deserving of monopoly protection. See *Mackay Radio*, 306 U.S. at 94 (the "mathematical expression" of "a scientific truth" is "not a patentable invention"); *Flook*, 437 U.S. at 595 n.18 ("an improved method of calculation, even when tied to a specific end use, is unpatentable subject matter"); *Bilski*, 130 S. Ct. at 3221. Prometheus's patents are precisely the sort of facially invalid claims that should be rejected at the threshold.

2. This Court recently explained that "[i]f a high enough bar is not set" for process patents—which "raise special problems in terms of vagueness and suspect validity"—"patent examiners and courts could be flooded with claims that would put a chill on creative endeavor and dynamic change." *Bilski*, 130 S. Ct. at 3229; see *Graham*, 383 U.S. at 9 (Thomas Jefferson, author of the 1793 Act, "insisted on a high level of patentability"). The Patent Office's proposal to dilute the Section 101 inquiry, and make patentability turn on application of Sections 102 and 103, would have precisely that harmful effect.

A "unique element" of the Section 101 inquiry is that it can often, as here, "be addressed by examining the four corners of a patent application"—a stark contrast to "evaluating novelty and nonobvious subject matter," which usually involves "searching a very large and often uncertain record of prior art" that invites mistakes. BOHANNAN & HOVENKAMP, CREATION WITHOUT RESTRAINT, ch. 5, at 14; see Am. Br. of Nine Law Professors at 34-36. The government concedes (at 11) that whether Sections 102 and 103 are satisfied depends on "fact-intensive" litigation.

Section 103 requires "factual inquiries" into all "the circumstances"—including the "scope and content in the prior art"; the "level of ordinary skill in the pertinent art"; "commercial success"; "long felt but unsolved needs"; and "failure of others"—inquiries fraught with administrative "difficulties" and a lack of "uniformity." *Graham*, 383 U.S. at 17-18. Similarly burdensome inquiries are necessary to determine novelty under Section 102. *E.g.*, *Schumer* v. *Lab. Computer Sys.*, 308 F.3d 1304, 1315-1316 (Fed. Cir. 2002). Not surprisingly, despite the government's view that the patents here show facial legal defects, Prometheus promises to "litigate all of these issues fully," arguing that their "complexity" makes them "'the most elusive'" questions in "'all of patent law.'" Prom. Br. 46-48. For the government to invite lengthy litigation over patents it concedes are invalid is contrary to sound antitrust policy. See *Walker Process Equipment, Inc.* v. *Food Mach. & Chem. Corp.*, 382 U.S. 172, 177 (1965).

The government's argument is doubly impractical because there is nothing comparable under Sections 102 and 103 to the well-developed body of

case law from this Court addressing the "natural phenomenon" issue at the heart of this litigation or expounding on what must remain in the "public domain" under Section 101. See *Bilski*, 130 S. Ct. at 3227; *id.* at 3258 (Breyer & Scalia, JJ., concurring). The poor fit of these provisions also is shown by the fact that the Patent Office granted the patents it now concedes "likely warrant invalidation" without perceiving any obstacle under Section 102 or 103. U.S. Br. 26.

The government's proposal to reduce Section 101 to a rubber stamp that is easily satisfied with clever drafting, and to have the federal courts grapple instead with complex inquiries that are difficult to resolve, is flatly at odds with Congress's goals in this year's America Invents Act, Pub. L. 112-29, 125 Stat. 284 (Sept. 16, 2011). Congress there responded to "a growing sense that questionable patents are too easily obtained" and "too difficult to challenge," and sought to "mov[e] in the direction of improving patent quality and making the determination of patent validity more efficient." H.R. REP. NO. 112-98, at 39 (June 1, 2011). In requiring "a more efficient system for challenging patents that should not have issued," it aimed to "limit unnecessary and counter-productive litigation costs." *Id.* at 39-40. A new procedure for post-grant review by the PTO that includes patent-eligibility under Section 101 is designed to minimize litigation burdens, and new fees provide the PTO with resources needed to weed out over-broad claims. *Id.* at 45, 48-50.

It is contrary to these goals to allow the PTO and the Federal Circuit to reduce the rigor of the Section 101 inquiry in a case of this kind. The government offers not a word in defense of Prometheus's patents.

It admits (at 8, 11, 27-29) that "the patents themselves make clear" there are "powerful arguments against affording patent protection to respondent's process." Yet after seven years of costly litigation, and two trips to this Court and the Federal Circuit, it argues that more judicial proceedings are necessary under Sections 102 and 103. In the future, as has happened in this case, the public would be exposed to monopoly overcharges and forgone medical services while decade-long litigation lumbers forward, contrary to the teaching of *Bell Atlantic* v. *Twombly*, 550 U.S. 544 (2007), *Celotex* v. *Catrett*, 477 U.S. 317 (1986), and the America Invents Act, all of which favor swift and efficient invalidation of defective patent monopolies. See *Brenner*, 383 U.S. at 532 (interpreting Patent Act to require invalidation in light of the "general intent of Congress, the purposes of the patent system, and the implications of a decision one way or the other").

The district court faithfully applied the Patent Act principles laid down by this Court when it granted summary judgment. Whether or not the Patent Office intends to apply Section 101 rigorously in its own proceedings, as Congress intends, it should not oppose efficient summary judgment proceedings in federal district court.

B. Prometheus's Patents Broadly Preempt Use Of A Natural Phenomenon.

Prometheus pretends its patents are "narrow and specific," apply only to "actual medical treatment," and do not preempt "fundamental concepts" or "any substantial activity." Br. 25, 32-33, 41-46. But it successfully advocated a far broader construction of its patents in the courts below. And the limitations Prometheus points to are illusory. As the

government observes (at 23), Prometheus's patents "preempt substantially all" of the "practical applications" of the correlations they describe.

1. Although the database used to develop these patents related only to pediatric gastrointestinal disorders, Prometheus concedes that its claims cover *all* autoimmune conditions. Br. 6-9. These include, in addition to gastrointestinal disorders, rheumatoid arthritis, lupus, hepatitis, diabetes, pernicious anemia, skin diseases, and a host of other conditions listed in the patents to "illustrate, but not limit" the scope of the claims. 2JA 13-14, 31-32; Pet. App. 51a, 75a; *e.g.*, 2JA 17, claim 22 (claiming method covering *any* non-gastrointestinal autoimmune disease).

Prometheus says the patents are narrow because some diseases are not covered. Br. 42-43; see U.S. Br. 22. But thiopurine drugs are immuno-suppressive, so the patent covers *all* autoimmune conditions that could be treated with the drugs except the narrow areas of organ transplantation and leukemia. See 1JA 27, 34. Prometheus cannot make natural correlations patentable by limiting its claims to one broad class of diseases. As *Bilski* explains, "*Flook* established that limiting an abstract idea to one field of use" does "not make the concept patentable." 130 S. Ct. at 3231; see *Diehr*, 450 U.S. at 193 n.14 ("A mathematical formula does not suddenly become patentable subject matter" by "limiting the reach of the patent" to "a particular technological use").

Confirming the broad sweep of its claims, Prometheus argues (at 43) that within the class of autoimmune diseases, physicians would have to invent radically new methods of calibrating metabolites to escape preemption. Using a standard blood test and

reaching their own conclusions—as physicians have done for decades—would not be lawful.

Given this broad preemption of all practical uses of the correlation between metabolites and health, Prometheus's amici attack a straw man when they argue that Mayo is challenging medical patents generally. We nowhere contend that Section 101 "excludes medical processes" (PhRMA Br. 8), "diagnostic and therapeutic methods" (BIO Br. 2), or patents involving correlations (AIPLA Br. 17). Mayo readily acknowledges the value of patent protection for innovations that "entail extraordinary risk and expense on the part of the pharmaceutical and biotechnology industries." PhRMA Br. 3-4. But the challenged patents here are invalid because they are uniquely abstract and expansive in their attempt to preempt a physical phenomenon. The rule that Justice Breyer embraced in *LabCorp* and that Mayo advocates here does not call into question patents that lack these pernicious features.

2. Prometheus also contends (at 43) that competitors are free to use numbers departing from its range by more than 15%. The government says doctors remain free to use higher correlations because "Crohn's disease patients may comfortably tolerate much higher 6-TG metabolite concentrations than those disclosed in the patent." U.S. Br. 22. But Prometheus successfully argued in the district court that its claims to levels "greater than" the number specified in the patents means the levels have no upper bound but reach "infinity." Sept. 29, 2005 Hearing Tr. at 49, D. Ct. Dkt. 605; see Pet. App. 96a-97a (holding that because "no upper limit is mentioned in the patents," "such limitation cannot be considered in construing the terms of the patent

claims," which cover "any level that is above about 400"); 2JA 17, claims 32-36 (there is no upper limit when thioguanine is administered).

Even under Prometheus's reasoning, its patents would prevent a physician from concluding that a 7000 6-MMP reading indicates too toxic a dose of these life-threatening drugs and that a 14% reduction in the maximum limit, to 6000, is necessary for patient safety. The tasks doctors and researchers have always performed in this fast-moving field—test blood and think freely about what the results mean—can now only be performed by paying Prometheus a fee.

3. Contrary to Prometheus's assertion (at 32) that the patents operate "in the context of patient treatment," claim 46 monopolizes the two-step process of determining metabolite levels and thinking about what that means for dosage. Prom. Br. 9 n.7. And Prometheus successfully argued to the district court—whose construction of the claims was adopted by the Federal Circuit—that the final step does not require *any* dosage change if a physician is notified that a dosage adjustment *may* be required. Pet. App. 109a; 1JA 13. Accordingly, only testing for metabolites and thinking about an appropriate dosage is required for infringement—exactly what a non-treating physician would do when conducting research.

Prometheus's attack on Dr. el-Azhary confirms that its claims are not limited to treatment. Prometheus concedes (at 11) that it alleged infringement based specifically on Dr. el-Azhary's research. Dr. el-Azhary's purpose in collecting data on metabolite levels was to study optimal levels for dermatology patients with autoimmune conditions. 1JA 17-18.

Metabolite levels for gastrointestinal disease were "irrelevant" to her. 1JA 19. But because Prometheus's claims applied to *all* autoimmune diseases and Dr. el-Azhary had *once* been sent a document identifying Prometheus's range (1JA 21, 38-39), Prometheus argued that she infringed when she thought about the best range for dermatology patients—"[w]hether she crumples [up the document], throws it away, reads it, acts on it, doesn't act on it, any assumptions you want." 1JA 42.

Dr. el-Azhary was deposed at length; forced to turn over confidential patient records; accused of infringing when she researched different ranges for dermatology patients; and dared not publish her results—which showed that the proper range for dermatology diseases was *vastly* different from Prometheus's ranges (Mayo Br. 13)—because Prometheus sought an injunction that would have covered that alleged infringement.

Prometheus runs away from these allegations now (at 11 n.12). For the first time in this litigation it says that Dr. el-Azhary did not infringe if she "ignored" or "disbelieved" Prometheus's numbers. That new standard, which is nowhere stated in the patents or found in the record, would inject a vague mental element into the issue of infringement and could not give any practical assurance to a physician. As Dr. el-Azhary testified at her deposition, once she knew of Prometheus's numbers, she could not "rule out" that she had them in mind when investigating whether other ranges were better for dermatological diseases. Sept. 21, 2006 Depo. at 96. Beyond this, the record is clear that Prometheus contended below—without any exceptions for "ignoring" or "disbelieving"—that once Dr. el-Azhary learned of

temperature. Here, as in *LabCorp*, the patents improperly monopolize a natural metabolic process. Prometheus's claims covering the physical phenomenon are not patentable simply because human intervention was necessary to develop and administer the drug.

2. Like the Federal Circuit, Prometheus (at 25-27) and the government (at 13-15) assert that thiopurine drugs "transform" a patient's body chemistry, testing for metabolites "transforms" the patient's blood, and the "transformative nature of the process as a whole" satisfies Section 101 even though the administering and determining steps—to which Prometheus made no contribution—are conventional steps that are necessary to observing the phenomenon. According to Prometheus (at 25), a process including these commonplace transformations "*necessarily* constitutes a concrete application" of scientific knowledge that satisfies Section 101—a return to "transformation" as the touchstone of patentability. But *Bilski* made clear that transformation is only a "clue" to patentability: not every transformation satisfies Section 101. 130 S. Ct. at 3225.

This is shown by *Flook*, where chemical transformations that occurred during the catalytic conversion of hydrocarbons did not save the broad claim invalidated there. Here too, the "transformations" the court identified are an exercise in labeling that bear no relationship to the purposes of the patent laws—the body itself produces the metabolites and blood testing is conventional. And these transformations do nothing to narrow the preemptive effect of the patents. As Justice Breyer has explained, using "virtually any natural phenom-

enon for virtually any useful purpose" involves "transforming matter." *LabCorp*, 548 U.S. at 136.

Prometheus says the transformations are "integral to the patents' core purpose" (Br. 26), but administering drugs and testing blood are commonplace data-gathering steps. And this Court has made clear that conventional data-gathering steps do not create a patentable process out of a natural phenomenon. See *Bilski*, 130 S. Ct at 3231 ("token" extra-solution components that provided "inputs into [an] equation" did "not make [a] concept patentable"); *Flook*, 437 U.S. at 590. Accordingly, this Court rejected a process patent that combined "the abstract idea of hedging risk in the energy market" with instructions to use "well-known random analysis techniques" to provide data inputs. *Bilski*, 130 S. Ct. at 3231. Similarly, Prometheus's addition of conventional administering and determining steps does not allow it to monopolize natural correlations just because those steps involve transformations of matter.

In fact, the two steps Prometheus added would be needed to make *any* use of the correlations. Without administering the drug and testing blood there would be no data to correlate. Thus, these steps are no limitation at all. See *In re Richman*, 563 F.2d 1026, 1030 (C.C.P.A. 1977) (steps that "merely determine values for the variables used" in making calculations "do not suffice to render the claimed methods, considered as a whole, statutory subject matter"); *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989) (rejecting under Section 101 claims that involved "performing clinical tests on individuals to obtain data"). The happenstance that these data-collection steps involve transformations should not

make them predicates for patentability because they are not inventive and do not narrow the preemptive sweep of the claimed monopoly.

Prometheus also points (at 27) to the use of "machines" to test blood, but it contributed nothing to the invention of those machines or to any new way to use them—exactly the situation in *Benson* and *Flook*. And their use is merely incidental to the claim covering natural correlations. Prometheus even argues (at 42) that because thiopurine drugs could be patented by their inventor as a "composition of matter," any process tied to those drugs must be patentable. But if "a tie to" any machine, transformation or composition of matter developed by others were enough to patent a physical phenomenon, any law of nature could be monopolized, contrary to this Court's decisions.

3. Prometheus's reliance (at 21, 27-28, 30) on Section 101(b), which defines "process" to include "a new use" of a machine or composition of matter, is completely misplaced because this definition does not alter the physical phenomenon rule laid down in *Flook* and *Bilski*. And thiopurine drugs and testing blood for metabolites are not "new uses." Prometheus concedes that physicians long have known that thiopurine metabolite levels provide "valuable information" about dosage; that technology to measure metabolites has long existed; and that its claims merely posit a contestable range of numbers for those metabolites. Prom. Br. 4, 11 n.13; 2JA 1-3, 10 col. 8:37-46, 19-21. Studies published years before these patents confirm that physicians across "North America" used and "value[d] these measurements." Summary & Reply, Cuffari *et al.*, *6-MP Metabolite Levels: A Potential Guide to Crohn's Disease Therapy*,

113 GASTROENTEROLOGY 690, 692 (1997); see Mayo Br. 5. Attaching particular numbers to a physical phenomenon and telling physicians to think about those numbers adds no "new use," but merely monopolizes what physicians already routinely do.

Contrary to Prometheus's and the government's arguments, Mayo does not contend that the "administering" and "determining" steps should be "ignored." But when the "claim as a whole" consists of nothing but these conventional steps plus a mental step of thinking about resulting numbers that the government concedes "add[s] no patentable weight" to the claims (U.S. Br. 28-29), it is clear that the claim *as a whole* is not patentable. See *LabCorp*, 548 U.S. at 137-138.

Under the government's and Prometheus's approach even laws of nature like $E=mc^2$ would be patentable. Simply combining that formula with a well-known computer program (a machine) or well-known process for isolating a sample of matter (a transformation) would satisfy Section 101. Because the law at first discovery was unknown and not obvious, Sections 102 and 103 would not stand in the way of a patent. But Einstein could *not* patent his original and valuable formula $E=mc^2$. *Chakrabarty*, 447 U.S. at 309. And it is absurd to suggest that Prometheus can patent "400=something to think about." Adding an ordinary blood test does nothing to elevate this open-ended mental step.

4. Prometheus's claims were not approved by Congress when it enacted 25 U.S.C. § 287(c). That provision cuts off remedies for infringement brought against "medical practitioners" and "affiliated entities" for the performance of a "medical" procedure. See Prom. Br. 57-58. Section 287(c) says nothing to

validate patent monopolies over observing how the human body responds to an external stimulus. It cannot be read to imply that Congress thought such patents proper. See *Bilski*, 130 S. Ct. at 3228-3229 (statutory defense specific to business method patents implies that there may be such patents but does "not suggest [their] broad patentability").

Vague references to "settled expectations" arising from the PTO having granted 150,000 patents for "methods of treating patients," or to particular medical patents, are also unavailing—the more so because the government admits that the PTO overlooked fatal defects in the patents it granted here. U.S. Br. 16; Prom. Br. 50-51. There is no reason to think that many granted patents claim broad preemption of a physical phenomenon, as Prometheus's do. And if some do so, the public is entitled to protection from them.[2]

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[2] For example, the patents at issue in *Arrhythmia* and *Abele* (Prom. Br. 47, 52) did not include a mental step that broadly precluded physicians from thinking about natural correlations. The claim in *Arrhythmia* "d[id] not encompass subject matter transcending what [the claimant] invented." 958 F.2d at 1059. The claim upheld in *Abele* did not include any mental step, and the court held *un*patentable another claim that preempted all uses of an algorithm. 684 F.2d at 908. *LabCorp* is the only case cited by Prometheus and its amici involving a similar patent.

Two recent Mayo patents cited by Prometheus (at 57) are different from its own overbroad claims. They focus on novel processes without preempting any natural phenomena. See U.S. Patent 7,981,612 (method involves performing traditional follow-up testing after making an initial determination with novel DNA testing); U.S. Patent 7,998,670 (process uses a novel man-made DNA probe that does not preempt any activity previously in the public domain). The third patent cited by

D. This Court's Decisions Require Invalidation Under Section 101.

The mental step in Prometheus's claims broadly precludes physicians from thinking about correlations produced naturally by the body in response to drugs—effectively barring new and improved testing in this rapidly changing field of medicine for twenty years. The government agrees with Mayo that this mental step "add[s] no patentable weight" to the claims, which otherwise consist of conventional steps employed in a conventional way.

Prometheus nonetheless relies on *Diehr* as supporting the patentability of its claims. But the contrast between the claims here and in *Diehr* could not be starker. The *Diehr* patent confined an equation within a particular manufacturing process which ensured that rubber molds were opened at the right moment to perfect the cure—a narrow but important solution to an industrial problem to which there is no equivalent in Prometheus's claims. Doctors knew how to administer drugs, test blood, and consider metabolite levels long before hearing from Prometheus. And rather than an open-ended claim on thinking about a biological correlation, the *Diehr* patent left others completely free to make different uses of the equation, with the result that there was no preemption of natural law.

This Court has never drawn a distinction between foreclosing use of "truly fundamental principles, in the abstract and across a broad range of potential endeavors and future applications," and

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Prometheus (at 51-52) expired in 2003. See http://tinyurl.com/3bn6u6g.

foreclosing most practical uses of a "natural phenomenon." Prom. Br. 37-39. To the contrary, it has repeatedly stated that "phenomena of nature" cannot be monopolized with broad claims because "they are the basic tools" of science. *Benson*, 409 U.S. at 67. Prometheus's effort to distinguish between "truly fundamental" and other laws of nature is unsupported in the case law, in which the scope of preemption of physical phenomena is key.

Here, as in *O'Reilly*—which prohibited Samuel Morse from expanding his patent on the telegraph to all uses of electric current for transmitting characters—Prometheus impermissibly claims "an exclusive right" to control anything a physician might do with metabolite correlations over a broad field, based on a narrow and highly disputable discovery. It impermissibly seeks to turn observation of metabolite levels in a database of pediatric Crohn's disease patients into a wide-ranging bar on physicians using their judgment in relation to dozens of diseases suffered by millions of people. See *Minerals Separation*, 242 U.S. at 271 (invalidating patent claims and holding that process patents "must be confined" to the "proportions" actually discovered). As in *Benson*, the "practical effect" of Prometheus's patents is that anyone who wishes to make use of the natural correlation between metabolite levels and the health of any patient with an autoimmune condition must pay Prometheus a license fee. It is effectively a patent on "the [natural correlation] itself," deterring further research—in what had been a fast-developing area—that could save lives. 409 U.S. at 71-72.

Prometheus treats *Flook* as a dead letter (at 29), "unequivocally rejected" in *Diehr*. But this Court

cited *Flook* repeatedly in *Bilski* as a guide to determining whether claims "are not patentable processes because they are attempts to patent abstract ideas." 130 S. Ct. at 3229-3230. The Court specifically endorsed the holding of *Flook* that when "an application's only innovation was reliance on a mathematical algorithm," embedding that algorithm in "'a particular technological environment'" and adding conventional extra-solution steps did not satisfy Section 101. And it applied that rule to strike down the inventor's business method claims. *Id.* at 3230-3231. As in *Bilski*, the claims here "add even less to the underlying [law of nature] than the invention in *Flook* did, for the *Flook* invention was at least directed to the narrower domain of signaling dangers in operating a catalytic converter." *Id.* at 3231. Prometheus's patents preempt even thinking about a biological correlation across the entire range of its practical application, for all patients taking immuno-suppressive drugs for virtually all auto-immune conditions.

Prometheus relies (at 39) on other cases that are irrelevant here because the patents, as in *Diehr*, narrowly confined a scientific principle within a process that left other uses freely available. The patentee in *Tilghman* "was the original discoverer of [a] process" for manufacturing fats and oils using specific applications of hot water under high pressure. 102 U.S. at 713. *Neilsen* upheld a patent on a mechanical apparatus for blowing hot air into a furnace, having discovered that hot air worked better than cold. See *id.* at 724-725; 151 Eng. Rep. 1266 (Exch. 1841). Bell's discovery of an apparatus that modulated electric current to reflect sound waves over a closed circuit left room for infinite other uses of electricity. *Telephone Cases*, 126 U.S. at 532-535.

Prometheus, by contrast, preempts all practical uses of the principle that thiopurine drugs, naturally converted by the body to metabolites, correlate with patient health and it insists that its patented numbers bar other researchers from offering cheaper tests with more accurate and useful information. *Flook* and *Bilski* hold that such sweeping preemption is inconsistent with Section 101.

E. Invalidating Prometheus's Patents Would Encourage, Not Hinder, Personalized Medicine.

New methods of testing or treating patients often are patent eligible. But combining existing drugs and blood testing with broad claims covering the relationship between drug metabolites and health does not pass muster. Sustaining Prometheus's patents would open the door to obviously abusive claims encompassing, for example, administering a drug, taking body temperature, and considering a change of dosage if body temperature exceeds 98.6 degrees. See AMA Am. Br. 12. Invalidating them under Section 101 would in no way call into question patents for innovative methods of treating patients, such as "new pharmaceuticals, medical devices" or "diagnostic testing kits," which are far removed from the instruction to think about physical phenomena at issue here. *Id.* at 10-11. Furthermore, this Court has not hesitated to reverse erroneous Federal Circuit interpretations of the Patent Act despite patentees' predictions that doing so would upset "millions of patents" and "tens of billions of dollars" in investment. *E.g.*, *KSR Int'l Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007); Br. of Respondent, No. 04-1350, at 15.

It is those inventions of new drugs, machines, or test equipment that require the incentives of a

patent monopoly, as amici and the literature Prometheus cites confirm. *E.g.*, Roche Am. Br. 7-11; FTC, EMERGING HEALTH CARE ISSUES 4 (2009); see PRESIDENT'S COUNCIL, PRIORITIES IN PERSONALIZED MEDICINE 21 (2008) (patent protection is necessary to encourage "large, high-risk R&D investments" in "novel medical products"; by contrast, an attempt to "patent diagnostic correlations" is "doubt[ful]" based on "Supreme Court cases"); Mayo Br. 49-50.

Prometheus says (at 53) that doctors using its methods can calibrate thiopurine dosages faster and cheaper than before. But Mayo investigated metabolite levels and proved Prometheus's numbers were wrong—Prometheus later abandoned its upper limit of 7000 for 6-MMP and adopted Mayo's 5700 limit. Dr. el-Azhary found that Prometheus's numbers were far in excess of safe levels for dermatology patients. Mayo sought to market a considerably less costly test based on its improved numbers, in obedience to the ethical mandate that physicians shall "do no harm." Prometheus would cut off those benefits to patients for twenty years based not on a large investment—it made none (Mayo Br. 4-6)—or on a significant discovery, but based merely on administering known drugs, testing blood using known methods, and observing a physical phenomenon that is part of the storehouse of knowledge open to all researchers. See SECRETARY OF HEALTH & HUMAN SERVICES' ADVISORY COMMITTEE REPORT 2 (finding *no* case in which a patent was necessary for development of a genetic test).

The district court properly applied this Court's precedents under Section 101 when it protected the public against this overreaching claim.

CONCLUSION

The judgment of the court of appeals should be reversed.

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AMICUS CURIAE BRIEF

No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES, DBA MAYO MEDICAL LABORATORIES, ET AL., PETITIONERS

v.

PROMETHEUS LABORATORIES, INC.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING NEITHER PARTY

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QUESTION PRESENTED

Whether an improved method of treating a patient with a man-made drug is ineligible for protection under 35 U.S.C. 101 because the therapeutic efficacy of the drug depends on the natural metabolic processes of the human body.

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ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF FOR THE UNITED STATES AS AMICUS CURIAE SUPPORTING NEITHER PARTY

INTEREST OF THE UNITED STATES

This case presents the question whether an improved method of treating a patient with a man-made drug is ineligible for protection under the Patent Act because the therapeutic efficacy of the drug depends on the natural metabolic processes of the human body. The Court's resolution of that question will significantly affect the work of the United States Patent and Trademark Office (PTO), which is responsible for issuing patents and advising the President on issues of patent policy. See 35 U.S.C. 2(a)(1) and (b)(8). The United States therefore has a substantial interest in the Court's disposition of this case.

STATEMENT

1. Certain gastrointestinal disorders, such as Crohn's disease, result from the abnormal functioning of the body's immune system. For decades, doctors have used a class of drugs known as thiopurines to treat these and other immune-mediated disorders by interfering with certain chemical reactions in the body on which the immune system depends.

Thiopurines are complex, synthetic chemicals that do not occur in nature. Invented and patented more than 50 years ago, the leading thiopurine drugs, 6-mercaptopurine (6-MP) and azathioprine (AZA), were immediately recognized for their utility in inducing the temporary remission of leukemia. See United States Patent Nos. 2,697,709 (1954) (claiming 6-MP and methods of its chemical synthesis, and noting its medical utility), 3,056,785 (1962) (same, AZA).[1] Doctors soon began to use the drugs as immunosuppressants in organ transplantation, and in 1962 a scientific paper described the use of 6-MP to treat ulcerative colitis, a type of immune-mediated gastrointestinal disorder. See Srikumar Sahasranaman et al., *Clinical Pharmacology and Pharmacogenetics of Thiopurines*, 64 Eur. J. Clinical Pharmacology 753, 754 (2008) (Sahasranaman). AZA and 6-MP are also associated with a variety of serious risks and side effects. See Sahasranaman 761-762; *Medical Toxicology* 1042-1043 (Richard C. Dart ed., 3d ed. 2004) (*Medical Toxicology*).

The immunosuppressive effects of AZA and 6-MP arise from the manner in which the drugs are metabolized by the human body. Upon ingestion, 6-MP is

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[1] The AZA patent describes the drug by its alternative chemical name, 6-(1-methyl-4-nitro-5-imidazolyl)-mercaptopurine.

converted by the natural chemistry of the body into various metabolites, including 6-thioguanine (6-TG) and 6-methyl mercaptopurine (6-MMP). Pet. App. 3a; see Sahasranaman 754-755. AZA converts in the body to 6-MP and is metabolized in the same fashion. Although the exact biological mechanism is not fully understood, it is believed that 6-TG interferes with the body's synthesis of certain DNA bases (purines) necessary to the production of lymphocytes, a type of white blood cell critical to the immune system. See *Medical Toxicology* 1042; Sahasranaman 754-755.

2. Respondent is the exclusive licensee of United States Patent Nos. 6,355,623 (2002) (the '623 patent) and 6,680,302 (2004) (the '302 patent), which claim methods of optimizing the dosage of thiopurine drugs in patients with auto-immune disorders based on the observed concentration of 6-TG and 6-MMP metabolites in the patient's blood. Pet. App. 2a-3a. The patents stem from the same priority application filed in 1998.

The patents acknowledge that the immunosuppressive qualities of AZA and 6-MP, as well as the efficacy of those compounds in treating auto-immune disorders, were well known in the art at the time of the original application. See, *e.g.*, '623 patent, col. 1, ll. 41-46. The patents also make clear that the metabolic breakdown of AZA and 6-MP in the human body, see *id.* col. 4, ll. 55-65; *id.* col. 5, ll. 17-39, the importance of the resulting 6-TG metabolites in producing the immunosuppressive effect of the drugs, *id.* col. 1, ll. 49-51, and the techniques necessary for measuring metabolite levels in a patient's blood, *id.* col. 9, ll. 12-65, were all understood in the prior art.

According to the inventors, however, the potential toxicity of thiopurine drugs and the difficulty of deter-

mining the correct dose for each patient made many doctors reluctant to prescribe them. See '623 patent, col. 1, l. 66 to col. 2, l. 7. The methods claimed in the '623 and '302 patents reflect the discovery that, in patients with certain immune disorders, a therapeutically effective but non-toxic dose of a thiopurine drug is a dose that yields a level of 6-TG metabolites in the patient's blood between 230 and 400 picomoles (pmol) per $8x10^8$ red blood cells, and a level of 6-MMP metabolites below 7000 pmol per $8x10^8$ red blood cells. *Id.* col. 3, ll. 31-41.

The Federal Circuit characterized claims 1 and 46 of the '623 patent as representative of the claims at issue in this case. Pet. App. 4a-5a. Claim 1 states:

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

'623 patent, col. 20, ll. 10-25. Claim 46 is similar, except that it dispenses with the "administering" step and claims only the step of "determining" 6-TG or 6-MMP levels "in a subject administered a [thiopurine] drug * * *, said subject having said immune-mediated gastrointestinal disorder." *Id.* col. 23, l. 42 to col. 24, l. 18.

3. Respondent markets a thiopurine metabolites test to clinics and hospitals for use in treating patients with immune-mediated gastrointestinal disorders. Consistent with the patented method, respondent's test reports the level of 6-TG and 6-MMP metabolites in the patient's blood relative to the claimed therapeutic range of 230 to 400 pmol/8x10^8 red blood cells. Petitioners initially purchased respondent's test but, in 2004, announced that they intended to begin marketing their own thiopurine metabolites test with somewhat different upper limits for therapeutic efficacy (450 pmol 6-TG and 5700 pmol 6-MMP). Pet. App. 5a-6a, 85a. Respondent, in its capacity as exclusive licensee, brought this suit for patent infringement.[2] *Id.* at 3a, 6a.

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[2] Respondent's status as the exclusive licensee (rather than the owner) of the patents-in-suit raises an issue of prudential standing that does not appear to have been addressed in the courts below. The '623 and '302 patents are assigned to Hospital Saint-Justine in Montreal, Quebec, Canada, which has not been named as a party to the lawsuit. This Court has held that "[t]he presence of the owner of the patent as a party is indispensable * * * to give jurisdiction under the patent laws" when an exclusive licensee brings an infringement suit. *Independent Wireless Tel. Co.* v. *Radio Corp. of Am.*, 269 U.S. 459, 468 (1926). Although *Independent Wireless* arose under a previous version of the Patent Act, the Federal Circuit "continues to adhere" to its holding, requiring that the patent owner be joined as a plaintiff unless the patent owner has assigned "all substantial rights under the patent" to the exclusive licensee and has thereby rendered the licensee "the effective 'patentee' under 35 U.S.C. 281." *Prima Tek II, L.L.C.* v. *A-Roo Co.*, 222

The district court granted partial summary judgment in respondent's favor on the issue of infringement. Pet. App. 115a; see *id.* at 84a-116a. The court construed the phrase "indicates a need" in the patents' "wherein" clauses to require that "when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required." *Id.* at 109a. Finding that the thresholds for toxicity in petitioners' test were sufficiently close to those disclosed in the patents, *id.* at 113a-114a, the district court concluded that petitioners' test "literally infringes all elements of the patents-in-suit," *id.* at 115a.

Petitioners subsequently filed a motion for summary judgment of invalidity under 35 U.S.C. 101. The district court granted the motion. Pet. App. 50a-83a. In so ruling, the court clarified its earlier interpretation of the "wherein" clauses in the disputed claims, construing the phrase "indicates a need" more broadly than respondent itself had urged. Respondent had contended that the patents required an affirmative written or oral warning to a physician about the treatment implications of the metabolite levels. 04-CV-1200 Resp. Opp. to MSJ at 18, 21 (S.D. Cal. Feb. 28, 2007); see Pet. App. 63a. The court rejected that construction, concluding that "it is the metabolite levels themselves that 'warn' the doctor that an adjustment in dosage may be required." *Ibid.*

The district court then declared the claims invalid under Section 101. Pet. App. 83a. The court held that "the patents-in-suit recite a natural phenomenon—the correlations between thiopurine drug metabolite levels

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F.3d 1372, 1377 (2000). Whether the patent owner here has assigned "all substantial rights" to respondent depends on the specific terms of the license agreement between respondent and the Hospital, which is not part of the record below.

and therapeutic efficacy and/or toxicity—and the claims 'wholly pre-empt' use of said correlations." *Ibid.* The court characterized the "administering" and "determining" steps of the claims as "merely necessary data-gathering steps for any use of the correlations," *id.* at 61a, and it observed that the efficacy of particular metabolite concentrations "results from a natural body process," *id.* at 66a. The court held that the patents impermissibly preempt that "natural" relationship because "the only practical use of the correlation is in drug treatment" and "anyone seeking to employ the correlation must conduct the only active steps recited in the claims." *Id.* at 75a.

4. The court of appeals reversed. Pet. App. 25a-49a. The court applied its then-exclusive "machine-or-transformation" test, under which a process is patent-eligible subject matter if it (1) "is tied to a particular machine or apparatus," or (2) "transforms a particular article into a different state or thing." *Id.* at 33a-34a (quoting *In re Bilski*, 545 F.3d 943, 954 (Fed. Cir. 2008) (en banc), aff'd on other grounds, 130 S. Ct. 3218 (2010)). The court held that the claims in the '623 and '302 patents "squarely fall within the realm of patentable subject matter" because, *inter alia*, they involve the administration of a drug to transform the patient's body chemistry for a concrete and useful end. *Id.* at 40a; see *id.* at 39a-42a. The court cautioned that "the only issue" before it was "whether the claims meet the requirements of § 101," and that respondent's appeal did "not raise any questions about lack of novelty, obviousness, or overbreadth." *Id.* at 39a.

Petitioners filed a petition for a writ of certiorari (No. 09-490). While that petition was pending, this Court issued its decision in *Bilski* v. *Kappos*, 130

S. Ct. 3218 (2010), which held that the machine-or-transformation test is not the sole test for determining the patent-eligibility of processes, *id.* at 3227. The Court then granted the petition in No. 09-490, vacated the court of appeals' judgment, and remanded for reconsideration in light of *Bilski*. 130 S. Ct. 3543 (2010).

5. The court of appeals again reversed the district court's judgment of invalidity and remanded for further proceedings. Pet. App. 1a-23a. Noting that this Court's decision in *Bilski* did not "dictate[] a wholly different analysis or a different result on remand," *id.* at 14a, the court reiterated its conclusion that respondent's patents are directed to transformative methods of altering a patient's body chemistry with specific drugs, *id.* at 16a-18a, and do not "merely claim[] natural correlations and data-gathering steps," *id.* at 16a. Although the court agreed with petitioners that the final "wherein" clauses "are mental steps and thus not patent-eligible per se," *id.* at 21a, it explained that "[a] subsequent mental step does not, by itself, negate the transformative nature of prior steps," *ibid.*

SUMMARY OF ARGUMENT

The court of appeals correctly held that respondent's patents are directed to patent-eligible subject matter —that is, subject matter that *could* be protected under the Patent Act if the "conditions and requirements" of Title 35 were otherwise satisfied. 35 U.S.C. 101. Petitioners have raised powerful arguments against affording patent protection to respondent's process. Properly conceived, however, petitioners' objections arise not under Section 101, but under the novelty and nonobviousness requirements of 35 U.S.C. 102 and 103. Al-

though the claims are likely invalid under those provisions, the claims describe patent-*eligible* subject matter.

I. A. The disputed claims describe a transformative physical process of (i) administering a man-made drug to a patient and (ii) determining from the concentration of certain metabolic byproducts in the patient's bloodstream whether the patient has received a therapeutically safe and effective dose. That is a classic patent-eligible process: it recites a series of acts, performed in the physical world, that transforms the subject of the process (the body chemistry of the patient) to achieve a useful result. The fact that the relevant physical transformation occurs within the human body does not cast doubt on the patent-eligibility of respondent's process, since the patent laws have long been understood to encompass improved methods of treating patients to alleviate medical disorders. Petitioners' suggestion (Pet. Br. 35-36) that the "administering" and "determining" steps may be ignored because they were well known in the prior art disregards this Court's repeated admonitions that the novelty of a claimed process is irrelevant to the Section 101 inquiry.

B. Contrary to petitioners' contention, respondent's claimed methods do not impermissibly preempt a "natural biological phenomenon" (Pet. Br. 23). First, the correlations at issue here are not "laws of nature," "physical phenomena," or "abstract ideas" in the sense in which those terms have been used in this Court's decisions. Thiopurine drugs are the synthetic products of human ingenuity: neither azathioprine nor 6-mercaptopurine nor any of their active metabolites occurs naturally in the human body, or indeed anywhere else in nature. The reaction of the human body to thiopurine drugs and their metabolites is a "natural"

correlation only in the sense that all drugs depend on the natural processes of the human body for their therapeutic effect. To treat that fact as a basis for denying patent protection would severely disrupt the operation of the patent laws.

Second, the claims do not preempt all practical applications of the relationship between thiopurine drugs and human health. If the allegedly "natural" correlation is described at an appropriately high level of generality (*e.g.*, "when thiopurine drugs are administered, the resulting metabolite levels in the patient's blood correlate with patient health"), there remain substantial opportunities to derive practical value from knowledge of that relationship without infringing respondent's patents. Petitioners' preemption claim is plausible only if the relevant correlation is described at a very fine degree of particularity. But because every useful invention could be described as exploiting a correlation between the attributes of the invention and some desired result, that approach would exacerbate the difficulties caused by treating the link between thiopurine metabolite levels and human health as a "law of nature."

II. Petitioners' fundamental objection to the disputed patent claims is that a doctor's mere mental inference, made at the conclusion of the processes described in the claims, is the only step that distinguishes the claimed processes from the prior art. See, *e.g.*, Pet. Br. 19, 24, 33-34. Although that fact does not render the claims invalid under Section 101, petitioners' argument has considerably more force under 35 U.S.C. 102 and 103, which require that a patentable invention be both novel and non-obvious. To be patentable over the prior art, a claimed process must recite new or different steps that alter what was done before. The "administering" and

"determining" steps of respondent's claimed processes were known in the prior art, however, and the "wherein" clauses merely describe the inferences a doctor could or should draw once those steps are completed. For purposes of patentability under Sections 102 and 103, those inferences cannot distinguish respondent's claimed processes from the prior art.

ARGUMENT

Petitioners contend that the claims at issue are invalid under 35 U.S.C. 101 because the physical processes they recite (*i.e.*, the administration of specified drugs and the determination of the patient's metabolite levels) have been "familiar to physicians for decades." Pet. Br. 36. Petitioners' ultimate conclusion that the claims are invalid appears to be correct. Contrary to petitioners' argument, however, the barrier to patentability is imposed not by Section 101 but by 35 U.S.C. 102 and 103, which require that a patentable invention reflect a novel and non-obvious advance over the prior art. Invalidation of the patents under Section 101, by contrast, could have untoward implications for future cases involving process patents that *do* satisfy Sections 102 and 103. Section 101 is, by design, a "coarse filter." PTO, *Interim Guidance for Determining Subject Matter Eligibility for Process Claims in View of Bilski v. Kappos*, 75 Fed. Reg. 43,922, 43,926 (July 27, 2010). The remaining provisions of the Patent Act permit the nuanced, fact-intensive distinctions necessary to separate patentable from unpatentable inventions.

The judgment of the court of appeals, which addressed only Section 101, therefore should be affirmed. On remand, the courts below can consider the application of Sections 102 and 103 (to the extent petitioners

have properly preserved challenges under those provisions), together with any other challenges petitioners may assert.

I. THE CLAIMED METHODS ARE PATENT-ELIGIBLE SUBJECT MATTER UNDER 35 U.S.C. 101.

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. 101. Section 101 marks the "threshold" of the patent system and "defines the subject matter that may be patented." *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3225 (2010). Congress purposefully cast the provision "in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts.'" *Diamond* v. *Chakrabarty*, 447 U.S. 303, 315 (1980); see *J.E.M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130-131 (2001) (*J.E.M. Ag Supply*).

This Court has recognized "three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 309). These are the "basic tools of scientific and technological work," *Gottschalk* v. *Benson*, 409 U.S. 63, 67-68 (1972), "free to all men and reserved exclusively to none," *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) (*Funk Bros.*). Those principles forbid two different but related types of patents.

First, a patent that expressly claims a law of nature, physical phenomenon, or abstract idea is invalid, no matter how important the discovery. Thus, "Einstein could not patent his celebrated law that $E=mc^2$; nor could

Newton have patented the law of gravity." *Chakrabarty*, 447 U.S. at 309. That conclusion follows directly from the text of Section 101, since neither the law that $E=mc^2$ nor the law of gravity is a "process, machine, manufacture, or composition of matter." 35 U.S.C. 101. Second, a patent that ostensibly claims patent-eligible subject matter, such as a machine or process, is nonetheless invalid if, in "practical effect," the patent would "wholly pre-empt" the public's access to unpatentable subject matter and operate as "a patent on the [idea or phenomenon] itself." *Benson*, 409 U.S. at 71-72. But if an inventor claims a "process which, when considered as a whole, is performing a function which the patent laws were designed to protect (*e.g.*, transforming or reducing an article to a different state or thing)," the mere fact that the invention exploits a law of nature or physical phenomenon—as all human endeavors must at some level—does not disqualify it under Section 101. *Diamond* v. *Diehr*, 450 U.S. 175, 192 (1981).

A. The Claims At Issue Here Recite A Patent-Eligible "Process"

1. A patent-eligible "process," in this Court's traditional formulation, "is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing." *Cochrane* v. *Deener*, 94 U.S. 780, 788 (1877); see *Diehr*, 450 U.S. at 183-184; *Benson*, 409 U.S. at 70. Although the Court recently clarified that this definition "was not intended to be an exhaustive or exclusive test," the Court reaffirmed that the transformative nature of a claimed method "is a useful and important clue, an investigative tool," for determining eligibility under

Section 101. *Bilski*, 130 S. Ct. at 3226-3227; see *id.* at 3232 (Stevens, J., concurring in the judgment) (noting that "the entire Court agrees" that "the machine-or-transformation test is reliable in most cases").

Claim 1 of the '623 patent recites a method comprising two affirmative steps: (1) "*administering* a drug providing 6-thioguanine to a subject," and (2) "*determining* the level of 6-thioguanine in said subject." Pet. App. 4a. Those steps describe a patent-eligible process under Section 101. The claim recites a series of acts in the physical world that achieve a useful end (treatment of auto-immune disorders) by transforming the body chemistry of the patient. As the process is performed, chemicals not naturally found in the human body (AZA and 6-MP) are combined (metabolized) with chemicals already in the body in order to interfere with other, undesired chemical reactions (formation of lymphocytes). The mixing of chemical substances for a useful result is a quintessential patent-eligible process. See, *e.g.*, *Tilghman* v. *Proctor*, 102 U.S. 707, 728 (1881) ("The mixing of certain substances together, or the heating of a substance to a certain temperature, is a process."). The "determining" step likewise involves the manipulation of a physical substance (the blood or tissue sample on which the metabolite test is performed). See Pet. App. 18a-19a; '623 patent, col. 9, l. 12 to col. 10, l. 14.

The "wherein" clauses—which the district court construed to require that the doctor "be warned that an adjustment in dosage may be required," Pet. App. 62a—do not diminish the transformative nature of the process as a whole. Those clauses describe the medical significance of the metabolic byproducts detected in the patient's blood after the transformations caused by the first step of the process. Although the "wherein"

clauses do not distinguish respondent's process from the prior art for purposes of 35 U.S.C. 102 and 103, see pp. 26-30, *infra*, they do not negate, and indeed are premised upon, the transformation of the patient's body chemistry that the administering step entails.

2. The fact that the relevant transformation takes place within the human body does not cast doubt on the patent-eligibility of respondent's claimed process. Methods of practicing the medical arts have long been viewed as "eligible to receive the protection of our patent laws." *Diehr*, 450 U.S. at 184. Shortly after the enactment of the 1952 Patent Act, for example, the Patent Office Board of Appeals (Board) upheld the patent-eligibility of a method of injecting medicine into the human body using a liquid pressure jet. See *Ex parte Scherer*, 103 U.S.P.Q. (BNA) 107 (Pat. Office Bd. App. 1954). Observing that "[t]he method claimed is of a character which would normally be regarded as within the field of patentable subject matter," *id.* at 109, the Board explained that "[c]laims involving treatment of the human body have been allowed on appeal" and that "[t]here is nothing in the patent statute which categorically excludes such methods," *id.* at 109-110. Indeed, as early as 1891 this Court considered a patent on a surgical method for preparing the root of a decayed tooth to receive an artificial crown. *International Tooth Crown Co.* v. *Gaylord*, 140 U.S. 55, 64 (1891). Although the Court rejected the patent for lack of novelty over the prior art, it did not suggest that methods of dental surgery were ineligible for patent protection. See *ibid.*[3]

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[3] The Commissioner of Patents declared in *Ex parte Brinkerhoff* that "[t]he methods or modes of treatment of physicians of certain diseases are not patentable." 24 Comm'r Manuscript Dec. 349 (July 5, 1883), *reprinted in* 27 J. Pat. Off. Soc'y 797 (1945). The rationale for

Methods of treating patients are now an integral part of the examination work of the PTO. According to agency databases, the PTO has granted more than 150,000 patents since 1952 that include at least one such claim. Congress has recognized that longstanding practice, establishing statutory limits on the remedies for infringement available against "medical practitioner[s]" with respect to certain medical procedures. 35 U.S.C. 287(c); cf. *Bilski*, 130 S. Ct. at 3228-3229 (construing Section 101 in light of Congress's enactment of a special defense to infringement of business-method patents in 35 U.S.C. 273). Respondent's claimed method for treating auto-immune disorders with thiopurine drugs is thus well within the accepted scope of patent-eligible subject matter.

3. Petitioners contend that, in analyzing the patent-eligibility of the claims under Section 101, the Court should disregard the "administering" and "determining" steps because those steps are "[w]ell-known" and have been "familiar to physicians for decades." Pet. Br. 36. In petitioners' view, the Section 101 inquiry should focus on the only alleged point of novelty in the patents: the specific concentration of thiopurine metabolites that correlates with patient health. See *id.* at 33-34.

Although many doctrines in patent law focus on an inventor's contribution over the prior art, this Court has specifically disapproved that mode of analysis in answering the threshold question of subject-matter eligibility

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that decision, however, was not a legal judgment that such methods were ineligible subject matter, but an empirical judgment that medical processes could not reliably produce consistent results. See 27 J. Pat. Off. Soc'y at 798. As medical science improved, the Patent Office gradually retreated from *Brinkerhoff*, eventually overruling it in 1954. See *Ex parte Scherer*, 103 U.S.P.Q. (BNA) at 110.

under 35 U.S.C. 101. The question "whether a particular invention is novel is wholly apart from whether the invention falls into a category of statutory subject matter." *Diehr*, 450 U.S. at 190 (internal quotation marks and citation omitted); see *id.* at 193 n.15. Although this Court at one time appeared to endorse petitioners' analytical approach, see *Parker* v. *Flook*, 437 U.S. 584, 591-594 (1978), it subsequently clarified that, for Section 101 purposes, "[i]t is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Diehr*, 450 U.S. at 188-189. The Court recently reaffirmed that principle in *Bilski*, explaining that *Diehr* "established a limitation on the principles articulated in * * * *Flook*" by "emphasiz[ing] the need to consider the invention as a whole" in performing the Section 101 inquiry. *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 188). The fact that the only physical steps claimed in respondent's patents were known in the prior art may well render those claims invalid under other provisions of the Patent Act, see pp. 26-30, *infra*, but it has no bearing on the method's patent-eligibility under Section 101.

B. The Claims Do Not Preempt All Practical Uses Of A Law of Nature or Physical Phenomenon

Petitioners contend that the disputed claims are invalid under Section 101 because they impermissibly preempt all practical applications of a law of nature or physical phenomenon—specifically, "the biological correlation between metabolite levels and health" (Pet. Br. 33). That contention fails for two reasons. First, the correlation is not a "law of nature" or "physical phenomenon" in the relevant sense because it exists only as the result of human intervention. Second, the claimed methods do

not preempt all practical uses of the relationship between metabolite levels and human health, at least if the correlation is described at an appropriately high level of generality.

1. a. The essential premise of petitioners' preemption argument is that the relationship between the administration of thiopurine drugs and the health of the patient—and, in particular, the concentration of 6-TG and 6-MMP metabolites that correlates with a therapeutic dose—is an unpatentable natural law. That premise is wrong. Neither azathioprine nor 6-mercaptopurine nor any of their active metabolites occurs naturally in the human body, or indeed anywhere else. Thiopurine drugs are the products of human industry, invented and patented more than 50 years ago.[4] See United States Patent Nos. 2,697,709 (1954) (claiming 6-MP and methods of its chemical synthesis, and noting its medical utility), 3,056,785 (1962) (same, AZA).

To be sure, thiopurine drugs depend for their therapeutic effect on the natural metabolic processes of the human body. The efficacy of *all* pharmaceutical compounds, however, depends on the body's natural reaction to artificial stimuli. More broadly, as the court of appeals observed, "quite literally every transformation of

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[4] One patented method of synthesizing 6-MP, for example, was as follows:

> A mixture of 18.5 g. hypoxanthine and 80 g. of phosphorus pentasulfide in 500 ml. of tetralin was heated at 200° for eight hours. The mixture was cooled and filtered. The solid residue, after being washed with petroleum ether and dried at room temperature, was boiled with 2 liters of water. The hot solution was filtered and the pH adjusted to 5 with ammonium hydroxide. Dark yellow crystals of 6-mercaptopurine hydrate precipitated on standing (12 g.).

United States Patent No. 2,697,709, col. 2, ll. 71-79 (1954).

physical matter can be described as occurring according to natural processes and natural law." Pet. App. 17a; cf. *Funk Bros.*, 333 U.S. at 135 (Frankfurter, J., concurring) ("Everything that happens may be deemed 'the work of nature,' and any patentable composite exemplifies in its properties 'the laws of nature.'"). The utility of every invention turns on its ability to produce a predictable chain of reactions leading to the desired result. If the "natural" character of that link were sufficient to trigger the "law of nature" exception to patent-eligibility under Section 101, the exception would swallow the rule.

b. It is therefore essential to apply the judicially crafted "law of nature" and "physical phenomenon" exceptions to Section 101 in a restrained manner and with an eye toward their animating purposes. This Court has applied those exceptions sparingly, and only to distinguish the pre-existing materials and principles of nature, to which all persons enjoy equal claim as the "basic tools of scientific and technological work," *Benson*, 409 U.S. at 67, from useful applications of those materials and principles, which may be the subject of a patent if the requirements of the patent laws are satisfied. 35 U.S.C. 101; see, *e.g.*, *Chakrabarty*, 447 U.S. at 313 (explaining that "the relevant distinction" under Section 101 is "between products of nature * * * and human-made inventions"); see also *J.E.M. Ag Supply*, 534 U.S. at 130.

The Court has thus affirmed the patent-eligibility of plants and bacteria that have been altered in useful ways through human ingenuity. In *Chakrabarty*, for example, the Court held that an otherwise normal bacterium that had been genetically altered to metabolize multiple components of crude oil was patent-eligible subject matter. The Court explained that the patentee's

discovery was "not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101." 447 U.S. at 310. Similarly, the Court held in *J.E.M. Ag Supply* that new varieties of corn created through the cross-breeding of plants selected by mankind for their desirable characteristics were eligible for protection under Section 101. 534 U.S. at 128, 145.

On the other hand, the Court has held that the "handiwork of nature" is unpatentable when it remains materially unaltered by mankind. *Funk Bros.*, 333 U.S. at 131. The Court likewise has indicated that patent-eligibility does not extend to "manifestations of laws of nature" such as "the heat of the sun, electricity, or the qualities of metals," *id.* at 130 (citing *Le Roy* v. *Tatham*, 55 U.S. (14 How.) 156, 175 (1853)), or "a new mineral discovered in the earth or a new plant found in the wild," *Chakrabarty*, 447 U.S. at 309.

The reaction of the human body to thiopurine drugs is not an unaltered "law of nature" or "physical phenomenon" in the relevant sense. Unlike the heat of the sun or the inherent qualities of metals, the correlation between 6-thiopurine metabolite concentrations and patient health exists *because* of human ingenuity, not antecedent to it. A patent directed to a physical phenomenon of that kind is not invalid under Section 101.

2. As framed by petitioners, the question presented in this case assumes that the disputed claims in the '623 and '302 patents "cover[] observed correlations between blood test results and patient health" and "effectively preempt[] all uses of the naturally occurring correlations." Pet. i. Even apart from the fact that the relevant "correlations" are not "naturally occurring," see pp. 18-20, *supra*, petitioners' preemption argument is plausible only if those correlations are described at a very

fine degree of particularity. That approach would exacerbate the problems caused by treating the human body's response to a foreign substance as a "law of nature" for purposes of the Section 101 exception.

a. The correlations implicated by the disputed patent claims could be described at a relatively high level of generality, *e.g.*, "when thiopurine drugs are administered, the resulting metabolite levels in the patient's blood correlate with patient health." Petitioners could not reasonably contend that respondent's patents preempt substantially all practical applications of that general insight. Thiopurine drugs have useful medical applications entirely apart from the treatment of the auto-immune disorders discussed in the '623 and '302 patents.

For example, physicians have used AZA for decades to suppress the immune rejection of kidney, heart, and other organ transplants. See *Medical Toxicology* 1042; Sahasranaman 754. Respondent's patents specifically exclude certain related uses of thiopurine drugs from the scope of the claimed methods. See '623 patent, col. 15, ll. 14-17 (excluding "diseases resulting from a graft versus host response" from the scope of the patent); '302 patent, col. 15, ll. 22-24 (same). Although the patents do not explain that exclusion, it likely reflects the inventors' awareness that the standard recommended dosages of AZA for organ-transplant patients—and thus the metabolite concentrations that correlate with patient health in that context—are much higher than those recommended for the treatment of auto-immune disorders. See *Medical Toxicology* 1042. In addition, 6-TG metabolites have important medical applications wholly unrelated to their immunosuppressive benefits, such as in the treatment of breast cancer. See, *e.g.*, Natalia Issaeva et al., *6-Thioguanine Selectively Kills BRCA2-Defective*

Tumors and Overcomes PARP Inhibitor Resistance, 70 Cancer Res. 6268 (2010) (discussing the utility of 6-TG metabolites in disrupting certain breast cancers). None of these applications of the relationship between 6-TG metabolites and patient health would infringe respondent's claims.

Even as to auto-immune disorders, moreover, there is no reason to believe that the claims encompass every practical application of the general relationship between thiopurine metabolite levels and therapeutic efficacy. For example, one study found that Crohn's disease patients may comfortably tolerate much higher 6-TG metabolite concentrations than those disclosed in the patents when the thiopurine drug that is administered is not AZA or 6-MP but tioguanine, a close chemical cousin that is likewise metabolized into 6-TG in the body. See K.R. Herrlinger et al., *Thioguanine-Nucleotides Do Not Predict Efficacy of Tioguanine in Crohn's Disease*, 19 Alimentary Pharmacology & Therapeutics 1269, 1271-1272, 1274 (2004) (reporting therapeutic 6-TG metabolite levels as high as 1241 pmol/$8x10^8$ red blood cells when using tioguanine, a concentration "much higher than described under therapy with standard thiopurines"). Thus, even if the general relationship between 6-TG metabolite levels and patient health were viewed as a "law of nature," respondent's patents would not preempt substantially all practical uses of that correlation.

b. Alternatively, petitioners could describe the relevant correlations in terms that essentially track the language of the patent, *e.g.*, "when thiopurine drugs are administered, 6-TG metabolite levels less than about 230 pmol per $8x10^8$ red blood cells correlate with insufficient efficacy in treating auto-immune disorders, while levels greater than about 400 pmol per $8x10^8$ red blood cells

correlate with undue risk of toxicity, and levels between those two numbers correlate with an appropriate balance between effectiveness and safety." If the correlations are described at that level of particularity, respondent's patents may preempt substantially all of their practical applications. Although the "administering" and "determining" steps ensure that the claims are not infringed by pure thought unaccompanied by action, those steps are essential prerequisites to most if not all practical applications of the specific numerical relationship described.

To allow "laws of nature" to be defined at that level of particularity would greatly exacerbate the problems caused by treating the body's response to synthetic drugs as a "natural" phenomenon. For any useful invention—*i.e.*, any invention that predictably produces beneficial results—the link between the precise characteristics of the invention and the desired results could be described, under that approach, as a natural correlation. And even the most narrowly drafted patent wholly preempts activity falling within its scope. To be sure, a patent could not be issued on the correlation itself (regardless of the level of specificity at which it was defined) because a correlation is not a "process, machine, manufacture, or composition of matter." 35 U.S.C. 101. But where, as here, a patent claims a transformative method that accords with established understandings of the statutory term "process" (see pp. 13-16, *supra*), invalidation under the "law of nature" exception should be reserved for very unusual circumstances.

In *Diehr*, for example, the Court held that the patent holders' claimed method of curing rubber, which relied on a pre-existing mathematical formula (the Arrhenius equation) to determine more precisely when the curing

press should be opened, was a patent-eligible process. See 450 U.S. at 177-179, 185-191. The Court explained, *inter alia*, that the patentees did "not seek to pre-empt the use of [the] equation," but instead sought "only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." *Id.* at 187. The invention in *Diehr* might have been said to reflect a correlation between use of the patentees' innovative technique and an increased likelihood of producing properly cured rubber. See *id.* at 178. But the Court's decision in *Diehr* is inconsistent with any suggestion that a patent can be held invalid on the ground that it preempts a correlation stated at that level of specificity.[5]

3. Petitioners rely (Br. 36-37) on Justice Breyer's separate opinion in *Laboratory Corp. of America Holdings* v. *Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) (*LabCorp*). *LabCorp* involved a method of diagnosing certain vitamin deficiencies by measuring the level of homocysteine, an amino acid, present in a patient's body fluid; an elevated homocysteine level indicated a deficiency of folate or cobalamin. See *id.* at 125 (Breyer, J., dissenting from dismissal of the writ). Based on the limited record that was before the Court, the government argued that the claim in *LabCorp* appeared to encompass all substantial practical applica-

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[5] This Court's prior discussions of the "law of nature" exception have referred to natural laws that are relatively broad and fundamental. For example, the Court's use of the "law that $E=mc^2$" and the "law of gravity" as examples of unpatentable laws of nature, *Chakraborty*, 447 U.S. at 309, suggests that the exception encompasses fundamental natural principles whose reservation for the exclusive use of a single patentee would cordon off large spheres of human endeavor. See also *Benson*, 409 U.S. at 68.

tions of a preexisting natural phenomenon. See U.S. Amicus Br. at 24, *LabCorp*, *supra* (No. 04-607).[6]

In both of the respects discussed above, the process claimed in this case is unlike the method at issue in *LabCorp*. First, homocysteine is naturally present in the body, and its relationship to folate and cobalamin deficiencies exists wholly apart from human intervention. By contrast, 6-TG metabolites are present in the bodies only of those persons who have been administered specific synthetic drugs. The correlation between homocysteine levels and folate/cobalamin deficiencies is thus a "natural" relationship in a way that the correlation between thiopurine metabolite levels and patient health is not.[7]

Second, the claim at issue in *LabCorp* appeared to encompass substantially all practical applications of even the very general understanding that an "elevated level of total homocysteine" suggests "a deficiency of cobalamin or folate." See 548 U.S. at 129 (Breyer, J., dissenting from dismissal of the writ) (citation omitted). The claim did not exclude any category of persons whose

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[6] The Court in *LabCorp* ultimately dismissed the writ of certiorari without deciding the validity of the claim under Section 101. See 548 U.S. at 125.

[7] Petitioners contend that this distinction is immaterial because respondent "did not invent" thiopurine drugs. Pet. Br. 37 n.7. But that objection misses the point: regardless of who first invented them, thiopurine metabolites (unlike homocysteine) do not occur in nature. Their relationship to human health is therefore not a "law of nature" in the relevant sense. And while processes involving the administration of "natural promoters" of biological changes may be patent-eligible in some circumstances (for example, injecting a patient with a natural substance not normally found in the human body), see *id.* at 38 n.7, the fact that respondent's patents use synthetic chemicals only underscores the error of petitioners' reliance on Section 101.

homocysteine levels had been tested, nor did it specify what level of homocysteine would be considered "elevated." Respondent's patents, by contrast, specifically exclude patients who have received thiopurine drugs (and thus have 6-TG metabolites in their bodies) to suppress certain immune responses to organ transplants. And because respondent's patents identify specific numeric ranges as reflecting a preferred balance between therapeutic effectiveness and avoidance of toxicity, they appear not to be infringed when doctors (after performing the "administering" and "determining" steps) consider the general relationship between metabolite levels and health but rely on substantially different numbers as defining the optimal ranges. See pp. 21-23, *supra*.

II. THE DISPUTED CLAIMS IN THE '623 AND '302 PATENTS ARE LIKELY INVALID UNDER 35 U.S.C. 102 OR 103

For the foregoing reasons, respondent's claims pass the "threshold test" of the patent system because they define a patent-eligible "process" that does not preempt any "law[] of nature" as the Court's Section 101 decisions have used that term. *Bilski*, 130 S. Ct. at 3225 (citation omitted). It does not follow, however, that the claims are valid. Petitioners' fundamental objection is that respondent's claimed process differs from the prior art only with respect to the mental inference a doctor may draw after the "administering" and "determining" steps have been completed. See, *e.g.*, Pet. Br. 19, 24, 33-34. Although that similarity to the prior art is irrelevant to the Section 101 inquiry, it would likely warrant invalidation of the claims under 35 U.S.C. 102 or 103.

Although petitioners attribute to the Federal Circuit the conclusion that the disputed patents comply with "federal patent law," Pet. Br. 22, the court of appeals

was careful to disavow that broad holding. The court explained that "the only issue" before it was "whether the claims meet the requirements of § 101," and that the appeal did "not raise any questions about lack of novelty, obviousness, or overbreadth." Pet. App. 39a. This Court should not resolve such questions in the first instance. The Court's analysis of the Section 101 question, however, should be informed by an understanding of the way in which other Patent Act provisions address petitioners' central objection to the '623 and '302 patents.

A. Section 102 provides that a person is not entitled to a patent if, *inter alia*, "the invention was known or used by others in this country * * * before the invention thereof by the applicant," or if the applicant "did not himself invent the subject matter sought to be patented." 35 U.S.C. 102(a) and (f). Section 103 withholds patent protection for inventions that, while novel, would have been obvious to a person skilled in the art at the time the invention was made. 35 U.S.C. 103(a). Here, the patents themselves make clear that the "administering" and "determining" steps of the disputed claims were part of the prior art, and that the inventors' only asserted innovation is the specific metabolite ranges cited in the "wherein" clauses of the claims. See, *e.g.*, '623 patent, col. 1, ll. 41-49, 66-67; *id.* col. 2, ll. 1-13; *id.* col. 9, ll. 12-18.

A patent applicant cannot, however, avoid a rejection under Section 102 or 103 merely by appending a purely mental step or inference to a process that is otherwise known in (or obvious in light of) the prior art. A "process" is a series of steps for achieving a useful result in the physical world. See, *e.g.*, *Cochrane*, 94 U.S. at 788. Here, the only affirmative steps described in the patent are (1) administering thiopurine drugs, and (2) deter-

mining metabolite levels. The district court construed the "wherein" clauses to require a kind of passive inference: the doctor must "be warned" of the medical significance of the metabolite levels. Pet. App. 62a. That is not a continuation of the process to be performed, but a description of how a doctor should interpret the result.

Such medical knowledge may be new, and it may be valuable. But identifying a new way in which the results of a prior-art process may be understood, or a new benefit that the pre-existing process may help its users to realize, does not create a new "process" that is entitled to separate patent protection. See *General Elec. Co.* v. *Jewel Incandescent Lamp Co.*, 326 U.S. 242, 249 (1945) ("It is not invention to perceive that the product which others had discovered had qualities they failed to detect."). [8] Rather, to be patentable over the prior art, a process claim must recite a series of steps in the physical world that differs from any series of steps that was previously known. Although a patent-eligible process may involve a "new use of a known process," 35 U.S.C. 100(b), as when a pre-existing process is incorporated into a new, larger series of steps, it does not satisfy Section 102 or 103 merely to identify new and useful inferences from the prior art. Because the "wherein" clauses of respondent's claims do not recite any physical step to be performed by a doctor (or anyone else), they add no

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[8] This does not mean that every process claim that recites a mental step is unpatentable. Claims that recite concrete processes with a "decision tree" structure (*e.g.*, "Perform steps A and B, and then do either C or D, depending on the results of A and B.") are both common and acceptable. In that sort of process, the mental step affects the physical steps to be performed. But the mere recitation of a mental inference at the *end* of a claimed process—in effect, a guide to interpreting the results—does not distinguish the process from the prior art.

patentable weight to the "administering" and "determining" steps.

That conclusion follows *a fortiori* from patent law's "printed matter" doctrine, under which the mere addition of novel printed matter to a product, such as instructions for using a device, does not add patentable weight. See, *e.g.*, *In re Ngai*, 367 F.3d 1336 (Fed. Cir. 2004).[9] If the district court had accepted respondent's argument that the "wherein" clauses require the laboratory performing the metabolite test to provide an explicit written or oral warning to the doctor, see pp. 6-7, *supra*, the PTO would have treated the content of any printed warning as irrelevant to patentability under the printed-matter doctrine. Likewise, if the claims had instead required the use of a medicine bottle for thiopurine drugs with the recommended metabolite range printed on the label, the PTO would have afforded the content of the label no patentable weight. If such explicit written statements of the optimal metabolite range would not have distinguished the claimed process from

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[9] This doctrine is the reason a newly published book is not patentable, even though a book (a man-made assembly of paper, glue, and ink) is a patent-eligible "manufacture" within the meaning of Section 101. Although differences between the printed matter contained in different books are obviously crucial for other legal (*e.g.*, copyright) and practical (*e.g.*, reading) purposes, they are irrelevant in the eyes of the patent law. Thus, while one who devises a new method of binding books might be entitled to a patent, the creator of new written content is not. Similarly, a process is not novel if it differs from the prior art only by including "wherein" clauses reciting the substantive medical significance of the results of the prior art process. See *King Pharms., Inc.* v. *Eon Labs, Inc.*, 616 F.3d 1267, 1278 (Fed. Cir. 2010) (method that was otherwise known in the prior art did not become patentable by adding the step of "informing" someone of an inherent property of that method because prior art method itself was unchanged).

pre-existing processes, a doctor's mental state of "be[ing] warned" (Pet. App. 62a) cannot have that effect.[19]

B. A practicing physician would use the information acquired through the "determining" step of respondent's claimed method to decide whether to adjust the patient's dosage or to maintain it at the original level. If the physician altered a patient's dosage based on the metabolite levels that the "determining" step revealed, he would presumably initiate a further "determining" step to ascertain whether the adjustment had produced the desired effect. In the world of actual medical practice, the process described in the '623 and '302 patents would thus be a part of a larger course of treatment; and that larger course of treatment might represent a meaningful (and potentially patentable) improvement over methods previously known in the art.

From a physician's standpoint, it may therefore be artificial to treat the "administering"/"determining" method claimed in the '623 and '302 patents as a discrete two-step process that culminates with the measurement of a patient's metabolite levels. The need to analyze the claims in that manner under the patent laws, however, results directly from the drafting choices made by the inventors (respondent's predecessors-in-interest). The

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[19] Under the reasoning set forth above, the claim at issue in *LabCorp* appears to have been invalid under Section 102 or 103, since that claim simply appended a mental "correlating" step to an "assaying" step that was already well known in the art. See 548 U.S. at 129, 136 (Breyer, J., dissenting from dismissal of the writ). The amicus brief for the United States in *LabCorp* argued that the claim appeared to be invalid under Section 102, although the brief discussed that question in terms of the claim's potential to remove pre-existing assaying methods from the public domain. See U.S. Amicus Br. at 28-30, *LabCorp*, *supra* (No. 04-607).

inventors could have attempted to distinguish the claimed process from methods known in the prior art by drafting the claims to include concrete treatment steps (the details of which presumably would have varied depending on the results of the "determining" step). Cf. note 8, *supra*. The inventors declined to do so, however, presumably because inclusion of such steps would have made it more difficult to prove infringement.[11] Indeed, in (successfully) arguing in the district court that petitioners' tests infringed the patents, respondent relied in part on the fact that the claims do not require an actual adjustment of drug dosage. See Pet. App. 108a. Such strategic trade-offs between claim scope and the risk of invalidity are common in patent prosecution, and respondent presumably made an informed appraisal of that risk in accepting an exclusive license under the patents.

C. By the same token, it might be viewed as exalting form over substance to deny under Section 101 relief to which petitioners are likely entitled under other provisions of the Patent Act. The only role of Section 101, however, is to identify the types of subject matter that may be *eligible* for patent protection if "the conditions and requirements" of Title 35 are satisfied. 35 U.S.C. 101. It is "a dynamic provision designed to encompass

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[11] Other factors influencing the patient's health, such as allergies or drug interactions, may sometimes induce a doctor not to adjust a patient's dosage even though the determined metabolite levels fall outside the optimal range as delineated in the '623 and '302 patents. And because liability for infringing a process patent generally requires proof that every step of the infringing conduct was attributable to the defendant, see 35 U.S.C. 271(a); *BMC Res., Inc.* v. *Paymentech, L.P.*, 498 F.3d 1373, 1378-1379 (Fed. Cir. 2007), adding a treatment step would make it more difficult to sue actors who do not themselves make treatment decisions.

new and unforeseen inventions." *J.E.M. Ag Supply*, 534 U.S. at 135.

The '623 and '302 patents describe a transformative method that falls squarely within the established understanding of the statutory term "process" and involves the administration of therapeutic compounds not found in nature. To hold that the method nevertheless falls outside Section 101 because its efficacy depends on the body's "natural" reaction to foreign substances would cast doubt on a host of patents for transformative medical processes that *are* novel and non-obvious. It would also exacerbate PTO's already formidable task of ensuring that more than 6500 patent examiners apply Section 101 in a predictable and consistent fashion. The remaining provisions of Title 35, which permit more nuanced factual distinctions, are the principal tools that Congress has provided for "drawing a line between the things which are worth to the public the embarrassment of an exclusive patent, and those which are not." *Graham* v. *John Deere Co.*, 383 U.S. 1, 9 (1966) (quoting Letter from Thomas Jefferson to Issac McPherson, Aug. 13, 1813, *in* 6 *Writings of Thomas Jefferson* 181 (Henry Augustine Washington ed., 1853)).

CONCLUSION

The judgment of the court of appeals reversing the district court's ruling under Section 101 should be affirmed.

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SEPTEMBER 2011

AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

SEP 2 - 2011
OFFICE OF THE CLERK

No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES)
AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

On Writ of Certiorari
To The United States Court of Appeals
For the Federal Circuit

BRIEF OF *AMICI CURIAE* AARP AND PUBLIC PATENT FOUNDATION IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICI CURIAE*[1]

Amicus AARP is a nonpartisan, nonprofit membership organization dedicated to addressing the needs and interests of people age 50 or older. AARP has a long history of advocating for access to affordable health care and for controlling costs without compromising quality. Affordable and quality health care is particularly important to the older population because of its higher rates of chronic and serious health conditions. Patents that claim medical correlations prohibit diagnosis and treatment, and discourage communication of medical information between a patient and physician. AARP works at the state and national levels for laws and policies that ensure greater freedom and competition in the healthcare marketplace. AARP supports this petition because allowing patents on pure medical correlations raises costs of and denies access to critical health services.

Amicus Public Patent Foundation ("PUBPAT") at Benjamin N. Cardozo School of Law is a not-for-profit legal services organization that represents the public interest in the patent system, and most particularly the public interest in protecting against the harms caused by undeserved patents and unsound patent policy. PUBPAT provides the

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[1] The parties have consented to the filing of this brief. In accordance with Supreme Court Rule 37.6, AARP and the Public Patent Foundation state that: (1) no counsel to a party authored this brief, in whole or in part; and (2) no person or entity, other than *amici*, their members and counsel has made a monetary contribution to the preparation or submission of this brief.

general public and specific persons or entities otherwise deprived of access to the patent system with representation, advocacy, and education. PUBPAT has argued for sound patent policy before this Court, the Court of Appeals for the Federal Circuit, various district courts, the United States House of Representatives, the United States Patent and Trademark Office (USPTO), the United Nations, the European Union Parliament, and other judicial, governmental and political bodies. PUBPAT has also requested that the USPTO reexamine specifically identified undeserved patents causing significant harm to the public. The USPTO has granted each such request. These accomplishments have established PUBPAT as a leading provider of public service patent legal services and one of the loudest voices advocating for comprehensive patent reform. PUBPAT supports petitioner because of PUBPAT's interest in ensuring that laws of nature like medical correlations are not patented.

SUMMARY OF ARGUMENT

Amici Curiae AARP and the Public Patent Foundation submit this brief in support of petitioners and reversal of the judgment of the United States Court of Appeals for the Federal Circuit because that judgment stems from the application of an approach to patentable subject matter that is inconsistent with this Court's precedent and with both health and patent policy. Allowing patents on pure medical correlations (i.e. that an overly high or low level of some chemical in the body correlates to an unhealthy condition) threatens doctors with claims of patent infringement should they discuss mere laws of nature with their patients, burdens the public with excessive health

care costs, and dulls incentives for real innovation in medical care.

The patenting of medical correlations – which are nothing more than expressions of laws of nature – has led to severe restraint on the provision of medical care and a greatly increased cost and reduced availability of vital medical services, damaging the public health of the nation. Federal Circuit decisions upholding medical correlation patents fail to abide by this Court's prohibition on the patenting of laws of nature. As a result, there are now countless patents on medical correlations, including the patent in this case and patents on correlating genetic mutations with a person's increased risk for a particular disease. The Federal Circuit has latched on to trivial steps beyond mental processes, such as the "administering" step in this case, to uphold patents that effectively preempt all uses of laws of nature. This is not a substantive analysis, but rather the application of a formulaic rule that saves any patent claim drafted with some "transformative" step – no matter how trivial. This directly conflicts with this Court's precedent that prohibits both the actual and effective patenting of laws of nature.

ARGUMENT

I. Medical Correlations Are Laws Of Nature And Thus Unpatentable.

The patenting of medical correlations, which are mere expressions of laws of nature, has led to severe restraint on the provision of medical care and a greatly increased cost and reduced availability of vital medical services, damaging the public health of

the nation. As just one example, medical correlation patents have been used to prevent patients contemplating surgery to remove their breast and ovaries from getting independent verification that they have genetic mutations corresponding to an increased predisposition for diseases affecting those body parts. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 2009 U.S. Dist. LEXIS 101809, *16-17 (S.D.N.Y. 2009) ("*AMP*") (owner of patents on medical correlations prevented patients from receiving medical services from physicians). But nature creates medical correlations, such as that between genetic mutations and predisposition for disease, not man. Thus, any patent that effectively preempts use of a medical correlation is invalid subject matter even if the patented correlation was only recently discovered by man. *Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584 (1978).

Rather than examine the effect of patents relating to medical correlations to determine whether they preempt all effective uses of the underlying law of nature, the Federal Circuit has instead relied on a formulaic rule to erroneously uphold medical correlation patents. As it did in this case, so long as there is some trivial "transformation of matter" included in the patent claim, the Federal Circuit holds that all concerns about patenting laws of nature disappear. It does no further analysis to see whether a law of nature is nonetheless being effectively preempted by the patent.

As a result, there are now countless patents on medical correlations, including the patent in this case and patents on correlating genetic mutations with an increased predisposition for a particular

disease. *See., e.g., AMP* (involving patents claiming the correlation between mutated BRCA genes and an increased propensity for developing breast cancer). According to the Federal Circuit, one can get a patent on correlating fair skin with an increased risk of sunburn, being a woman with an increased risk of becoming pregnant, and being elderly with an increased risk of suffering from Alzheimer's disease so long as some trivial step involving a transformation of matter is added.

In an attempt to abide by this Court's guidance in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), the Federal Circuit held in the *AMP* gene patent case that the challenged correlation claims there, which contained "only abstract mental processes," were ineligible subject matter. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 2011 U.S. App. LEXIS 15649, at *67 (Fed. Cir. July 29, 2011) ("We conclude that Myriad's claims to 'comparing' or 'analyzing' two gene sequences fall outside the scope of § 101 because they claim only abstract mental processes"). However, in doing so, it continued to apply its strict rule that is easily circumvented by adding any trivial non-mental step to a patent claim. *Id.* Thus, while the Federal Circuit reached the correct result in *AMP*, finding the correlation claims involving "only abstract mental processes" were invalid, it did so by continuing to follow the same improper test that it applied in this case, which condones medical correlation patents that have the effect of preempting all uses of an underlying law of nature, even if they are not purely abstract.

By completely failing to protect laws of nature from patents that effectively proscribe all use

thereof, the Federal Circuit's rule is contrary to this Court's long established precedent that prohibits the patenting of laws of nature. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (citations omitted). This Court has repeatedly held that laws of nature cannot meet the threshold for qualifying as "inventions patentable" under 35 U.S.C. § 101 because "[s]uch discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Id.* quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948). "[T]he reason for the exclusion is that sometimes too much patent protection can impede rather than 'promote the Progress of Science and useful Arts,' the constitutional objective of patent and copyright protection." *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126-27 (2006) (J. Breyer, dissenting).

This Court has also repeatedly rejected formulaic rules on issues in patent law, particularly what constitutes patentable subject matter. *Bilski* (rejecting the Federal Circuit's "machine or transformation" test for patent eligibility). Despite this, the Federal Circuit below again retreated to implement a formulaic rule-based analysis, finding as patentable subject matter anything that involves a transformation of matter, regardless of whether that transformation is central to the patented invention or whether the claim effectively preempts all uses of the underlying law of nature.

The "administering" step at issue in this case is of trivial importance, as there is no requirement in the claims of the patent in this suit that the amount of drug being administered cause any chemical change in the patient to whom the drug is being

administered. 2 J.A. 16 (U.S. Pat. No. 6,355,623, cl. 1).

This is in stark contrast to most pharmaceutical patents that require a "therapeutically effective amount" of a drug be administered. Here, the "administering" step may result in no change whatsoever to the patient's condition, but the Federal Circuit nonetheless latched on to it to uphold the patent as not being on a law of nature. This was not a substantive analysis, but rather the application of a formulaic rule that any transformation of matter – no matter how trivial – is sufficient to make a claim patent eligible, regardless of whether the claim still preempts all pragmatic uses of a law of nature.

Had the Federal Circuit correctly applied the pragmatic preemption analysis mandated by this Court, it would unquestionably have found that the claim has the practical effect of preempting all uses of the law of nature that underlies the claim, namely that between the presence of certain metabolite levels and the presence of a drug. That medical correlation is not an invention of the patentee. It is the result of nature's handiwork. But the existence of the patent forecloses all effective use by others of the law of nature. Thus, it is unpatenable under this Court's precedent.

CONCLUSION

For the foregoing reasons, the decision of the Court of Appeals should be reversed.

September 9, 2011

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (d/b/a MAYO MEDICAL LABORATORIES) and MAYO CLINIC ROCHESTER,

Petitioners,

—v.—

PROMETHEUS LABORATORIES, INC.,

Respondent.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF THE AMERICAN CIVIL LIBERTIES UNION AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF AMICUS[1]

The American Civil Liberties Union ("ACLU") is a nationwide, nonprofit, nonpartisan organization with more than 500,000 members dedicated to the principles of liberty and equality embodied in the Constitution and this nation's civil rights laws. Since its founding in 1920, the ACLU has frequently appeared before this Court in cases involving the First Amendment, both as direct counsel and as *amicus curiae*. Although this case arises under patent law, it also raises fundamental issues regarding freedom of thought and scientific inquiry that implicate important First Amendment values. The proper resolution of this case is, therefore, a matter of significant concern to the ACLU and its membership throughout the country.

STATEMENT OF THE CASE

This is a challenge to a series of patent claims on the grounds that the claims reach unpatentable subject matter. As described by the Federal Circuit, the patents "claim methods for determining the optimal dosage of thiopurine drugs used to treat gastrointestinal and non-gastrointestinal auto-immune diseases." Pet. App. 2a. What that means in practice is made clear by the language of the actual claims. For example, Claim 1 of Patent 623 states as follows:

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[1] The parties have lodged blanket letters of consent to the filing of *amicus* briefs with the Clerk of the Court. No counsel for a party authored this brief in whole or in part, and no person other than *amicus curiae*, its members or its counsel made a monetary contribution to its preparation or submission.

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Pet. App. 4a.[2]

In other words, the patent holder, Prometheus, claims a method patent consisting of the following steps: (1) administer a drug; (2) determine the effect of the drug by measuring the metabolite levels in a patient's blood through an unspecified test; and (3) consider whether to adjust the dosage of the drug in light of the effect it had on the patient's metabolite level.

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[2] Some of the claims at issue do not include the first, "administering" step. Pet. App. 4a-5a.

Prometheus does not base its assertion of infringement on a patent on any of the drugs covered by Step 1, nor on a patent on the test referenced in Step 2. And Step 3, on its face, refers only to a thought process; it may contemplate but does not expressly cover any additional action beyond reviewing the test results and thinking about their impact on the patient's therapeutic plan.

The district court found the patents invalid. As an initial matter, it concluded that the first two steps of the challenged method claim merely provide the background information necessary to assess whether the dosage of thiopurine should be adjusted. Pet. App. 63a. It then concluded that the correlation between metabolite levels in the blood and the efficacy/toxicity of thiopurine is not patentable for several interrelated reasons: first, consideration of the correlation is best understood as a "mental step" or thought process; second, the correlation itself is a natural phenomenon occurring within the body and not invented by the patent holder; and third, the patent claims preempt use of the correlation. Pet. App. 63a-78a.

The Federal Circuit reversed in an opinion issued prior to this Court's decision in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). Pet. App. 25a. Applying its "machine or transformation test," the Federal Circuit upheld the challenged patents on the theory that Steps 1 and 2 – administering thiopurine and determining metabolite levels – transform the body. In the circuit court's view, that transformation by itself is sufficient to make the entire claim patentable, even though Prometheus is not alleging infringement based on the drugs administered in

Step 1 or the metabolite test used in Step 2, and even if the correlation between metabolite levels and drug efficacy could not be independently patented because it involves nothing more than a thought process and natural phenomenon. Pet. App. 39a-48a. After this Court remanded the case in light of *Bilski*, the Federal Circuit reaffirmed its prior holding based on the same rationale. Pet. App. 14a. This Court again granted certiorari.

SUMMARY OF ARGUMENT

The patent claims in this case are invalid under the well-established principle that a patent cannot be issued over an abstract idea or a natural phenomenon. These claims amount to a patent on the correlation between metabolite levels in the blood and the efficacy of thiopurine drugs, which is both an abstract idea and a natural phenomenon.

The Federal Circuit held the claims patentable by focusing on two steps in the claims that consist of administering a drug and then performing a test to determine the effects of the drug. However, the essence of the claims is found in the third step: mentally considering what to do once the effects are determined. This Court's opinions on the patentability of abstract ideas and natural phenomena can best be understood as requiring that the Court look past steps added by drafters in an effort to achieve patentability and instead focus on the essence of the claim. When that analysis is performed in this case, it is clear that the claims are invalid.

The claims are also invalid under the First Amendment. The First Amendment has not

traditionally been applied to patent claims, but the principle that you cannot patent abstract ideas is not only compatible with the First Amendment, but compelled by it.

The First Amendment principle that abstract ideas cannot be patented applies, moreover, regardless of whether the abstract idea represents the essence of the patent claim. Here, the third step of the challenged claim prohibits what both courts below aptly described as a "mental step" – namely, whether the metabolite levels of a patient's blood indicate a need to change the dosage of thiopurine drugs. Because the First Amendment does not allow the government to patent thought under any circumstances, the decision below must be reversed.

ARGUMENT

I. THE CHALLENGED CLAIMS PATENT ABSTRACT IDEAS AND NATURAL PHENOMENA, AND ARE THEREFORE INVALID UNDER SECTION 101.

Section 101 of the Patent Act provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," is eligible to obtain a patent if "the conditions and requirements" of the Patent Act are otherwise met. 35 U.S.C. § 101.

It has long been understood that the language of Section 101 does not reach abstract ideas or natural phenomena, which are not patentable. *Bilski*, 130 S. Ct. at 3225. What is less clear is how to determine whether a patent claim that includes abstract ideas and/or natural phenomena, like those

at issue in this case, is nonetheless patentable because of other elements in the claim.

When confronted with that problem in the past, this Court has focused on the essence of the claim and determined patent eligibility on that basis. *Amicus* acknowledges that the Court's opinions have not been explicit in that focus; we nonetheless believe that it is the best way to reconcile the relevant decisions, particularly this Court's instruction to analyze the claim "as a whole."[3] *Diamond v. Diehr*, 450 U.S. 175, 188 (1981); *Parker v. Flook*, 437 U.S. 584, 594 (1978).

Adoption of this pragmatic approach allows the Court to see through clever drafting that otherwise obscures what lies at the heart of the claim. *Diehr*, 450 U.S. at 192. A key component of the Court's inquiry into a claim's essence is to determine whether the claim preempts or has the "practical effect" of patenting a thought or natural phenomenon. *Gottschalk v. Benson*, 409 U.S. 63, 72 (1972). When a claim has preempted others from using an abstract idea or law of nature, the Court has invalidated it. *Bilski*, 130 S. Ct. at 3231. Employing this reasoning, the Court has rejected patents that at their essence claim natural phenomena or abstract ideas, even when they superficially appear, based on the insertion of

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[3] The Federal Circuit has referred to the essence of the claim in making Section 101 determinations. Pet. App. 20a (describing the "essence" of the claim at issue in *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989)); *In re Comiskey*, 554 F.3d 967, 981 (Fed. Cir. 2009); *In re Nuijten*, 500 F.3d 1346, 1357 n.7 (Fed. Cir. 2007) (describing claim at issue in *In re Alappat*, 33 F.3d 1526 (Fed. Cir. 1994)).

limitations or extrasolution steps, to be patent eligible. *Id.* at 3229-30.

Once these principles are applied to the challenged patents, they do not survive Section 101. The insertion of Steps 1 and 2 into the patent claim – administering a drug that Prometheus has not patented and then measuring its effect on the blood through a test that Prometheus has also not patented – cannot and does not alter the fact that the essence of the claim is the correlation between thiopurine drugs and metabolite levels in the blood. That correlation constitutes both an unpatentable abstract idea and natural phenomenon, as the district court recognized and the Federal Circuit did not dispute. This conclusion is reinforced by the preemptive effect of the claims on mental consideration of what a metabolite level suggests about drug efficacy, as well as on use of the naturally-occurring correlation in medical practice.

A. This Court's Precedent Makes Clear That Section 101 Requires Examination Of The Essence Of The Claim And Whether The Claim Has The Practical Effect Of Patenting An Abstract Idea Or Natural Phenomenon.

As this Court reiterated most recently in *Bilski*, patent law does not grant proprietary rights over laws of nature, products of nature, physical or natural phenomena, and abstract ideas. *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010). *See also Diamond v. Chakrabarty*, 447 U.S. 303, 309-10 (1980). This core understanding of patent law is 150 years old, *Le Roy v. Tatham*, 55 U.S. 156, 174-75

(1852), is directly tied to the constitutional mandate that patents "promote the Progress of Science," *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126-27 (2006) (Breyer, J., dissenting), and reflects the recognition that these non-patentable subjects represent "the basic tools of scientific and technological work." *Benson*, 409 U.S. at 67. Because laws of nature, natural phenomena, and abstract ideas are "part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none," *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948), they do not qualify as patentable inventions under 35 U.S.C. § 101.

In deciding whether a proposed patent describes a genuine invention or an abstract idea, this Court has said that Section 101 imposes "[t]he obligation to determine what type of discovery is sought to be patented." *Flook*, 437 U.S. at 593. In other words, the Court has looked to the essence of the claim to determine whether it is truly an invention or simply an unpatentable idea. *See Diehr*, 450 U.S. at 191-92. A determination of patentable subject matter that depends "simply on the draftsman's art," the Court has noted, "would ill serve the principles underlying the prohibition against patents for 'ideas' or phenomena of nature." *Flook*, 437 U.S. at 593. Thus, the Court has dismissed efforts to insert limitations or steps in patents that do not convert what is claimed into a true invention. The prohibition against patenting abstract ideas "cannot be circumvented by attempting to limit the use of the formula to a particular technological environment" or adding insignificant extrasolution activity, such as data-

gathering steps. *Diehr*, 450 U.S. at 191-92; *see also Bilski*, 130 S.Ct. at 3231 ("limiting an abstract idea to one field of use or adding token postsolution components did not make the concept patentable").

The Court's key cases illustrate this pragmatic approach. *Bilski*, *Benson*, and *Flook* all rejected patent claims that at their essence covered abstract ideas. The Court dismissed attempts to justify patentability based on limitations to a particular technological field, *see Bilski*, 130 S. Ct. at 3231 (claims on abstract idea of hedging risk limited to use in commodities and energy markets) and *Benson*, 409 U.S. at 71-72 (claims on formula limited to use with digital computer). Likewise, the Court dismissed attempts to justify patent eligibility based on the addition of extrasolution activity, *see Bilski*, 130 S. Ct. at 3231 (claims included instructions for using well-known analysis techniques to help establish inputs into the hedging equation) and *Flook*, 437 U.S. at 590 (claims included post-solution activity of adjusting the alarm limit to the figure computed according to the formula).

Preemption of an abstract idea or law of nature has been a crucial factor in determining invalidity. Because the *Benson* algorithm had "no substantial practical application" except in connection with the digital computer, the claim's limitation to use with a computer was meaningless. 409 U.S. at 71-72. "[T]he patent would wholly preempt the mathematical formula and in practical effect would be a patent on the algorithm itself." *Id.* at 72. Similarly, the *Bilski* court found that the patent claims at issue covered the abstract concept of hedging risk and thus "would preempt use of this

approach in all fields, and would effectively grant a monopoly over an abstract idea." 130 S. Ct. at 3231. In contrast, the method for curing synthetic rubber at issue in *Diehr* that relied on a mathematical formula was patentable because the patent holders "do not seek to pre-empt the use of that equation." 450 U.S. at 187. The equation could be applied with respect to other processes that did not involve the numerous steps detailed in the claim: installing rubber in a press, closing the mold, constantly determining the temperature of the mold, constantly recalculating the appropriate cure time through use of the formula and a digital computer, and automatically opening the press at the proper time. *Id.*

These cases make clear that, though the machine-or-transformation test is "a useful and important clue" as to process patentability, it is far from an "exhaustive or exclusive test." *Bilski*, 130 S.Ct. at 3226-27. The Court in *Bilski* chose to reject the Federal Circuit's adoption of the machine-or-transformation test as the sole test for process patents under Section 101, a ruling it need not have reached given the circuit court's finding of invalidity. Such a rigid test, however, could not be reconciled with the analysis of *Benson*, *Flook*, and *Diehr*, particularly because it is entirely possible for a natural phenomenon to inherently involve transformation – *e.g.*, aging. Indeed, chemical "transformations" occurred during the claimed catalytic chemical conversion of hydrocarbons in the *Flook* method found invalid by the Court. 437 U.S. at 586, 596-98.

Dissecting a claim to determine whether a "transformation" exists in one or more steps, and ending the Section 101 inquiry at that point, departs from this Court's focus on the essence of what is claimed. Patents must be examined to determine whether, once extrasolution steps and technological field limitations are stripped away, abstract ideas or natural phenomena are the essence of the claim, and whether the claim's practical effect is to preempt what is unpatentable.

B. The Challenged Patents Claim the Abstract Idea of Considering A Patient's Metabolite Level And The Natural Correlation Between That Level And Drug Efficacy And Toxicity.

In light of this precedent, the court below erred in its Section 101 analysis. Rather than considering the claims as a whole for their essence, the Federal Circuit's conclusion was rooted in the flawed assumption that the "claim as a whole" analysis could be satisfied by the addition of data-gathering steps that could be characterized as involving "transformation" to an otherwise mental process. This Court's precedent clearly establishes that simply including technological field limitations – such as the context of autoimmune and gastrointestinal diseases – and extrasolution steps – such as administering a drug and measuring its effects – does not allow claims on natural phenomenon and abstract ideas to survive Section 101 scrutiny. The appellate court compounded its error by misapprehending the claims' preemptive

effect on thought and naturally-occurring medical correlations.

The Federal Circuit misconstrued this Court's admonition to analyze the "claim as a whole," in deciding that claims containing data-gathering steps that involve some "transformation" satisfy Section 101. It focused on what it deemed to be transformative in the first two steps and discounted the centrality of the mental steps in the wherein clauses, because "[t]he data that the administering and determining steps provide for use in the mental steps are obtained by steps well within the realm of patentable subject matter." Pet. App. 21a. However, the fact that two of the steps might involve "transformation" does not resolve the patentable subject matter question, especially when whatever "transformations" occur in these steps are not central to what is patented. As Justice Breyer explained in the context of *Metabolite*: The patented process "instructs the user to (1) obtain test results and (2) think about them. Why should it matter if the test results themselves were obtained through an unpatented procedure that involved the transformation of blood? Claim 13 is indifferent to that fact, for it tells the user to use any test at all." 548 U.S. at 136.

Like *Metabolite*, and as in *Benson*, the claims here are "not limited to any particular art or technology, to any particular apparatus or machinery, or to any particular end use." *Benson*, 409 U.S. at 64. The steps of administering a drug and determining metabolite levels are not limited to a particular methodology, nor tied to particular machinery. Furthermore, the claims do not direct a

particular end use by reciting, for example, a third step of administering a certain dosage of a specified drug in response to the metabolite levels that are found. It is entirely possible to infringe on the claims by carrying out the administering and determining steps, thinking about the significance of the resultant level, and doing nothing more. While Prometheus attempts to frame the claims here as directed at optimizing treatment of a disease, the claims do not mandate any action by the physician after considering the natural correlation.

The Federal Circuit's discussion of *Grams* highlights its misplaced focus on "transformations" in the first two steps. The invalidated *Grams* claim was on a process of performing a clinical test on an individual and determining, by using an algorithm, if an abnormality existed and its possible causes. *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989). In its effort to distinguish *Grams*, the *Prometheus* court noted that the *Grams* clinical test was just to "obtain data." Pet. App. 20a. The court opined that the claim would have survived had it recited the "performing of clinical tests on individuals that were transformative – and thus rendering the entire process patentable subject matter.'" *Id.* (citing *Grams*, 888 F.2d at 840). According to the Federal Circuit, therefore, had the *Grams* claim been slightly modified, so that it specified a clinical test that could be deemed "transformative" – like the routine assaying of blood found to be transformative by the court in *Prometheus* – it would have been patentable. Its Section 101 analysis myopically zeroes in on any type of "transformation" in the claim, one that could be manufactured by attorneys in drafting, while failing to determine the essence of the claim. As the Court

has said, such an interpretation "exalts form over substance." *Flook*, 437 U.S. at 590.

This error is particularly troubling in the medical context, where it is easy to draft claims that require a "transformative" determination of the existence of a natural phenomenon in order to claim the natural phenomenon itself. "Indeed, to use virtually any natural phenomenon for virtually any useful purpose could well involve the use of empirical information obtained through an unpatented means that might have involved transforming matter." *Metabolite*, 548 U.S. at 136 (Breyer, J., dissenting). Should the Federal Circuit's opinion stand, it would send a clear message to patent applicants: So long as you include a step that involves processing a sample to determine a concentration of a substance, even though the method of processing is routine and well-known in the field, the claim will survive Section 101.

The challenged claims also cannot cross the Section 101 threshold because they preempt a physician from considering whether the test drug dosage was too high or low – an abstract idea – and from using the medical correlation between the patient's 6-thioguanine level and the efficacy of thiopurine drugs – a natural phenomenon – in considering whether to adjust the dosage. In this case, the evidence established that the correlation has no known practical use other than the context described in the claim – treatment for gastrointestinal or autoimmune disease. Pet. App. 75a-77a. Thus, Prometheus' argument that the correlation could be used with respect to other diseases is entirely speculative. As in *Benson*, the

correlation between the metabolite levels and drug efficacy have "no substantial practical application" except in the context of these diseases, and for that reason, the patent preempts the naturally-occurring correlation. *Benson*, 409 U.S. at 71. This correlation was not invented by the patent holder. And it cannot be invented around because how a dosage of a thiopurine drug will be metabolized by a patient is a natural phenomenon, one that varies patient by patient.

Furthermore, the claims preempt abstract thought. Any physician who receives a patient's metabolite levels and thinks about their significance is subject to liability. The Federal Circuit found otherwise, asserting without further explanation that a physician who only evaluates the resulting metabolite level, without carrying out the administering and determining steps, would not infringe. Pet. App. 21a-22a. Yet, courts have found that physicians would be in violation of a patent for considering test results, and the laboratories that provided the results have been held liable for inducing physicians to infringe. In *Metabolite*, Lab. Corp. was found liable for performing the test and educating doctors about the medical correlation; the doctors who review test results and "automatically reach a conclusion about whether or not a person was suffering from a vitamin deficiency" were also infringing. 548 U.S. at 130.

The likelihood of infringement liability for physicians who simply consider the test results illustrates the preemptive effect of these claims. Presented with a patient's 6-thioguanine level, a doctor risks liability merely by thinking about

whether the level calls for an increase, decrease, or continuation of a drug dosage. Indeed, Mayo's researcher was accused of ongoing infringement because, while studying skin conditions, she previously had received a report containing the therapeutic ranges claimed by Prometheus. Pet. for a Writ of Cert., *Mayo Collaborative Servs. v. Prometheus Labs., Inc.* 8-9 (2011) (No. 10-1150). Even though she no longer received reports that included the ranges, they were in her memory, and so she continued to infringe in respondent's view. *Id.* The patents claim the exclusive right to thinking about a patient's metabolite levels and their relationship to drug efficacy. This erodes physicians' ability to provide quality patient care and threatens to stifle innovation. *See Metabolite*, 548 U.S. at 138.

Accordingly, because these claims patent the abstract idea of considering adjustment of a drug dosage in light of a patent's metabolite levels and the natural correlation between metabolite levels and drug efficacy and toxicity, they are invalid under Section 101.

II. THE FIRST AMENDMENT LIMITS THE REACH OF CONGRESS' POWER UNDER THE INTELLECTUAL PROPERTY CLAUSE.

Prometheus in this case is attempting not only to patent an abstract idea – the fact that thiopurine drugs affect metabolite levels in the blood – but also the mental process involved in thinking about how altered metabolite levels should affect a patient's drug dosage. As noted above, that claim is invalid as a matter of patent law. But there is more involved in this case than merely patent law. The principle that

government may not license abstract ideas or regulate freedom of thought is central to the First Amendment. Thus, even if the Patent Act were construed to allow the patent claims in this case, the First Amendment would prohibit it. By construing Section 101 to bar the patent claims in this case, the Court can and should avoid the constitutional problems that would otherwise arise if the decision of the Federal Circuit were affirmed. *See, e.g., Skilling v. U.S.*, 130 S.Ct. 2896, 2929-30 & n.40 (2010); *NLRB v. Catholic Bishop of Chicago*, 440 U.S. 490, 500-01 (1979).

A. The First Amendment Prohibits The Patenting Of Abstract Ideas.

The structure of intellectual property is created by Article 1, section 8, clause 8, which covers copyrights and patents: Congress has the power "To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." Like other legislative powers conferred on Congress by Article I, the power to award copyrights and patents is limited by the First Amendment.

In copyright, where the potential conflict between copyright law and the First Amendment is more obvious, various doctrines, such as fair use, or the distinction between idea and expression, exist to accommodate the First Amendment's values. Although these doctrines are incorporated into the copyright statute, the Court has suggested that these doctrines are required by the First Amendment. *Harper & Row, Publrs. v. Nation Enters.*, 471 U.S.

539, 555-560 (1985); *Eldred v. Ashcroft*, 537 U.S. 186, 219 (2003).

The doctrine of patent law that abstract ideas and natural laws are not patentable is based on interpretation of the Patent Act, but has not been previously described as compelled by the First Amendment. 35 U.S.C. § 101. However, the "abstract idea" doctrine that is central to this case – and strikingly similar to the idea/expression distinction in copyright – protects fundamental First Amendment values. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981) ("excluded from such patent protection are ... abstract ideas."); *Eldred*, 537 U.S. at 219.

Here, the essence of Prometheus' claims is the idea that certain lab results may indicate a need to change the thiopurine dosage. It is, in that respect, no different than saying, "if your headache doesn't go away, consider taking a second aspirin." At best, this observation simply describes the natural phenomena that have taken place in the body and/or the abstract idea that certain test results indicate the drug has not reached maximum effectiveness. At worst, the claim is essentially prohibiting a physician from thinking "I need to change the dosage."

Freedom of thought lies at the very core of the First Amendment. Indeed, freedom of speech and belief would be meaningless without it. Granting Prometheus or any other patent holder a monopoly on abstract ideas is incompatible with a constitutional regime that protects freedom of thought. In this case, the language of the challenged claims makes that connection explicit. What Prometheus seeks to monopolize through its patents

is the right to think about the correlation between thiopurine drugs and metabolite levels, and the therapeutic consequences of that correlation. The patents, if upheld, would also presumably prevent a medical researcher from discussing the correlation (if the researcher had also administered the drug and measured its impact) with her colleagues, or at a professional conference, or in a published paper.

The First Amendment does not permit that result. The ability to think without constraint is an essential attribute of human autonomy and an essential cornerstone of the First Amendment. *See* Laurence Tribe, AMERICAN CONSTITUTIONAL LAW, § 12-1 (2d ed. 1988); Thomas Emerson, THE SYSTEM OF FREEDOM OF EXPRESSION 6 (1970). In Justice Harlan's words, "No other approach would comport with the premise of individual dignity." *Cohen v. California*, 403 U.S. 15, 24 (1971). Or, as Justice Brandeis famously stated in an opinion joined by Justice Holmes, the First Amendment protects the "freedom to think as you will and to speak as you think." *Whitney v. California*, 274 U.S. 357, 375 (1927) (Brandeis, J., concurring).

Echoing that theme, *Palko v. Connecticut*, 302 U.S. 319, 326-27 (1937), described "freedom of thought and speech" as "the matrix, the indispensable condition, of nearly every other freedom." *See also Stanley v. Georgia*, 394 U.S. 557, 564-66 (1969); *Griswold v. Connecticut*, 381 U.S. 479, 482 (1965) ("The right to freedom of speech ... includes not only the right to utter or to print, but the right to ... freedom of inquiry, freedom of thought ... "); *U.S. v. Reidel*, 402 U.S. 351, 355-56 (1971). More recently, in *Ashcroft v. Free Speech Coalition*,

535 U.S. 234, 253 (2002), the Court stated that, "First Amendment freedoms are most in danger when the government seeks to control thought or justify its laws for that impermissible end. The right to think is the beginning of freedom . . . ."

The Patent Clause of Art. 1, § 8 undoubtedly provides a compelling interest in granting an exclusive license on properly patentable items. However, there can be no compelling interest in granting an exclusive license on abstract ideas or every possible expression of those ideas. Even in copyright, the government does not claim a compelling interest in licensing an idea or every possible expression of that idea.

The same First Amendment principles apply to patent law. Assume, for example, that the government decided that the way to encourage mathematical innovation was to grant specific universities exclusive rights to study specific fields of mathematics. There can be no serious doubt that such exclusivity would be unconstitutional. Indeed, the First Amendment is based on exactly the opposite conclusion – that progress is best achieved through a marketplace of ideas that cannot exist if thought is strictly controlled.

In upholding the patents in this case, the Federal Circuit misapplied patent law and misapplied the First Amendment.

B. The First Amendment Prohibits Patents That Prevent A Person From Thinking A Particular Thought.

The patents in this case would be unconstitutional under the First Amendment even if the

Federal Circuit were correct that the essence of the patents did not involve an abstract idea. That is because Step 3 of the claim still describes what the Federal Circuit acknowledged is a "mental step," which is to say a thought. Pet. App. 21a.

As Prometheus' own expert explained to the district court, once a physician reads the results of the test ordered at Step 2, the physician would be infringing if he "crumples it up, throws it away, reads it, acts on it, doesn't act on it, any assumptions you want to come up with." 1JA 42. The wherein clauses are obviously intended to alert the physician to act in a therapeutic setting, but the claim is not limited to the therapeutic setting or to any action taken as a result of the test levels. No physician having ordered the administration of the drug and the test may think about whether to increase or decrease dosage without permission from the patent holder.

Whatever patent law allows in these circumstances, the First Amendment does not permit the government to control thoughts, whether it does so directly through regulation or by delegating that authority to a private party through the grant of a patent.. As a matter of First Amendment law, moreover, it is immaterial whether the constraint on thought is ultimately characterized as essential to the patent claim. Even incidental restrictions on speech (let alone thought) are unconstitutional if they are directed at the suppression of ideas or content-based. *United States v. O'Brien*, 391 U.S. 367 (1968). This patent claim is both.

Assuming other patent criteria are met, a patent can, of course, be granted on a drug. It can be

granted on an otherwise patentable method of administering a drug. It can be granted on an otherwise patentable method of testing for the effectiveness of the drug. It cannot be granted on thinking about the results of the test. That is true even if the patent claim is a method claim that includes all of these steps. If any portion of a claim restricts a person's ability to think about a specified subject, it is unconstitutional under the First Amendment. Because the final step in this claim does exactly that, it is invalid.

An analogy may be helpful. Assume Henry Ford obtained a patent on the process of the moving assembly line consisting of first having one person put on the hood and then, after the body of the car has been moved by a conveyor belt, a second person put on the trunk. Assume that is a patent eligible process. Assume further that General Motors obtained a patent on the same hood-trunk process by adding a third step, "wherein if the process takes more than 5 minutes consider whether to reverse the order." Applying the Federal Circuit's transformation analysis, the hood-trunk "transformative" steps would justify General Motors' claim if other patent law criteria were satisfied, even though the third step describes pure thought. In our view, the First Amendment prohibits such a patent even if patent law does not.

Under this hypothetical patent, General Motors' engineers could think about reversing the order in which parts are assembled based on the speed of the assembly line. Personnel at Ford, or any other plant, who engaged in the same "mental step" would be infringing the patent. This case presents

precisely the same situation. Prometheus personnel who administer the drug and the test can look at the results and think about the dosages. Researchers who are simply reviewing dosage studies can think about dosages. People at Mayo can lawfully administer the drug and the test. But, people at Mayo cannot look at the results and think about the dosages.

All patents of course begin with a thought, but thought itself is not patentable. The principle that private thoughts are beyond government control is so basic to our constitutional scheme that we are unaware of any case in which the authority to control pure thought has been at issue. In this context, however, the absence of direct precedent merely highlights the extraordinary nature of the asserted claim.

A patent that explicitly targets and restricts thought cannot be reconciled with the First Amendment.

CONCLUSION

For the reasons stated above, the judgment of the court of appeals should be reversed.

Respectfully submitted,

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Dated: September 8, 2011

AMICUS CURIAE BRIEF

No. 10-1150

In The Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES)
AND MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF *AMICI CURIAE* THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN MEDICAL ASSOCIATION, THE AMERICAN HOSPITAL ASSOCIATION, THE AMERICAN SOCIETY OF HUMAN GENETICS, THE ASSOCIATION OF AMERICAN MEDICAL COLLEGES, THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE ASSOCIATION OF PROFESSORS OF HUMAN AND MEDICAL GENETICS, THE COLLEGE OF AMERICAN PATHOLOGISTS, THE FLORIDA HOSPITAL ASSOCIATION, THE MINNESOTA HOSPITAL ASSOCIATION, AND THE MINNESOTA MEDICAL ASSOCIATION IN SUPPORT OF PETITIONERS

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INTEREST OF THE *AMICI CURIAE*

Amici curiae submit this brief in support of petitioners Mayo Collaborative Services (d/b/a Mayo Medical Laboratories) and Mayo Clinic Rochester (collectively "Mayo") because the judgment of the Federal Circuit in this case stems from an interpretation of patentable subject matter that is inconsistent with this Court's constitutionally grounded precedent and with public policy regarding both innovation and health care.[1]

Amici are associations of physicians, researchers, medical educators, and other providers of healthcare-related services. *Amici* are concerned with the potential impact of patent claims covering natural phenomena, such as the correlations covered by Prometheus's patents. Such patents have great potential to impede the development and practice of medicine and raise health care costs.

The American College of Medical Genetics (ACMG) is a private, non-profit, voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral-level medical geneticists and other physicians involved in the practice of medical genetics. With more than 1,500 members, the

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[1] The parties have consented to the filing of this brief. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amici curiae* and their members or their counsel made a monetary contribution to its preparation or submission.

ACMG's mission is to improve health through the practice of Medical Genetics. In order to fulfill this mission, the ACMG strives to 1) define and promote excellence in medical genetics practice and the integration of translational research into practice; 2) promote and provide medical genetics education; 3) increase access to medical genetics services and integrate genetics into patient care; and 4) advocate for and represent providers of medical genetics services and their patients. The position of the ACMG is that observations of naturally occurring correlations should not be patentable.

The American Medical Association (AMA) is the largest professional association of physicians, residents and medical students in the United States. Additionally, through state and specialty medical societies and other physician groups seated in its House of Delegates, substantially all U.S. physicians, residents and medical students are represented in the AMA's policy making process. The objectives of the AMA are to promote the science and art of medicine and the betterment of public health. The AMA joins this brief on its own behalf and as a representative of the Litigation Center of the American Medical Association and the State Medical Societies. The Litigation Center is a coalition among the AMA and the medical societies of each state, plus the District of Columbia, whose purpose is to represent the viewpoint of organized medicine in the courts.

The American Hospital Association (AHA) represents nearly 5,000 hospitals, health care systems,

and networks, plus 37,000 individual members. AHA members are committed to improving the health of communities they serve and to helping ensure that care is available to, and affordable for, all Americans. The AHA educates its members about health care issues and advocates to ensure that their perspectives are considered in formulating health care policy.

The American Society of Human Genetics (ASHG) is a non-profit, tax-exempt organization that consists of more than 7,200 professionals in human genetics including researchers, clinicians, academicians, ethicists, counselors and other medical professionals. ASHG serves members by providing forums to share study results (the annual meeting and the Society journal); enhancing genetics education by preparing future professionals and the public; and promoting genetic services. As ASHG members transfer new knowledge to the next generation of genetics professionals and the public, new ideas will be translated into improved clinical practice. ASHG is concerned that claims covering patenting of natural phenomena will impede research and the development of improved medical practice, particularly in genomic or personalized medicine.

The Association of American Medical Colleges (AAMC) is a non-profit organization representing all 135 allopathic medical schools in the United States, about 400 major teaching hospitals and health systems, and about 90 academic and professional societies representing nearly 110,000 faculty members. AAMC's member institutions are at the forefront of

medical education, research and research training, and health care innovation and delivery. AAMC members perform nearly 55% of the extramural research sponsored by the National Institutes of Health, and they partner with industry in discovering new and better approaches to the diagnosis, treatment, and prevention of human diseases. The AAMC is committed to the continuing improvement of health care and the Continuing Medical Education of physician practitioners based on sound scientific evidence.

The Association for Molecular Pathology (AMP) is an international medical professional association representing approximately 1,900 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. AMP dedicates itself to the development and implementation of molecular diagnostic testing, which includes molecular genetic testing in all its definitions, in a manner consistent with the highest standards established by CLIA, the College of American Pathologists, the American College of Medical Genetics, and the FDA. AMP members work in widely diverse settings: academic medical centers, independent medical laboratories, community hospitals, public health laboratories, government agencies, and the *in vitro* diagnostics industry. AMP members are involved in every aspect of molecular diagnostics: research and development, administration and interpretation of molecular tests, policy and regulation, and education.

The Association of Professors of Human and Medical Genetics (APHMG) is a non-profit organization that promotes human and medical genetics educational programs in North American medical and graduate schools. Currently more than 90 medical and graduate schools are members. The APHMG represents the faculty members that teach human and medical genetics to virtually all medical students in North America. As educators, they teach medical students to think about, diagnose and treat genetic diseases. It is the APHMG's position that all physicians must be free to think broadly, creatively, analytically and without fear that they risk infringing a patent merely by *thinking* about the relationship between certain treatments and their potential metabolic and clinical sequelae.

The College of American Pathologists (CAP) is the world's largest medical society composed exclusively of pathologists, with nearly 18,000 members. Pathologists are physicians who examine tissues, blood, and other body fluids for the purposes of medical diagnosis and patient care. Through its accreditation and proficiency testing programs, the CAP is also a leader in assuring the quality of laboratory testing. More than 7,000 laboratories are accredited by the CAP, and approximately 23,000 laboratories are enrolled in the College's proficiency testing programs.

The Florida Hospital Association (FHA) is a voluntary association comprised of 185 hospitals and health systems, and 16 Professional Membership Groups that include 1,300 professional members from

across the state of Florida. The FHA has a common goal of providing the highest quality of care to the patients served by its members. Through effective and proactive advocacy, FHA demonstrates the community value of hospitals, builds consensus with other groups, and secures necessary resources so its members can continue to provide needed critical care to their communities.

The Minnesota Hospital Association (MHA) represents the interests of hospitals in the State of Minnesota, including 146 community-based hospitals and 16 health systems. MHA assists Minnesota hospitals – and their employed and affiliated health care providers – in carrying out their responsibilities to provide quality health care services to their communities; promote universal health care coverage, access, and value; and coordinate development of innovative health care delivery systems.

The Minnesota Medical Association (MMA) is a professional association representing approximately 11,000 physicians, residents, and medical students in the State of Minnesota. The MMA seeks to promote excellence in health care, to insure a healthy practice environment, and to preserve the professionalism of medicine through advocacy, education, information and leadership. For more than 150 years, the MMA and its members have worked together to safeguard the quality of medical care in Minnesota as well as the future of medical professionalism.

SUMMARY OF ARGUMENT

New drugs and new tools for diagnosing illness and monitoring treatment are critical to the advancement of medicine. The patents at issue in this case, however, do not claim innovative drugs or new diagnostic tools. Instead, these patents grant exclusive rights over the mere observation of natural, statistical correlations between certain metabolite levels in the body, as measured by well-known means, and the potential toxicity and effectiveness of well-known drugs. If these patents remain in force, any physician who measures those metabolite levels and knows about the observed correlations will unavoidably become an infringer. Thus, these patents convert routine, sound medical practice into prohibited infringement.

If such claims to exclusive rights over the body's natural responses to illness and medical treatment are permitted to stand, the result will be a vast thicket of exclusive rights over the use of critical scientific data that must remain widely available if physicians are to provide sound medical care. Conscientious physicians will be unwilling and unable to avoid considering all relevant scientific information when reviewing test results. Thus, as medical knowledge accumulates, patent licenses increasingly will be required for physicians to conduct even well-established diagnostic tests. Laboratories will risk indirect infringement merely by educating doctors about advances in scientific understanding. It is hard to imagine how the clinical diagnostic community will

continue to provide quality patient care and how physicians will continue to practice medicine in an ethical and effective manner under such a regime.

Moreover, the claims at issue run afoul of this Court's longstanding ban on patenting "laws of nature, physical phenomena, and abstract ideas," *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)). That prohibition implements the constitutionally grounded policy that patents may be granted only to "Inventors" so as to "promote Progress in . . . the useful Arts." U.S. Const. art. I, § 8, cl. 8.

The patentable subject matter inquiry therefore must consider whether an applicant who has discovered a natural phenomenon or come up with an abstract idea is the *inventor* of a patentable application of the phenomenon or idea, rather than the competent draftsman of a merely conventional application. *Parker v. Flook*, 437 U.S. 584, 590 (1978). Thus, in evaluating whether claim terms such as Prometheus's "administering" and "determining" steps are "insignificant" additions to claimed natural phenomena or abstract ideas, *Bilski*, 130 S. Ct. at 3230 (quoting *Diamond v. Diehr*, 450 U.S. 175, 191-92 (1981)), courts must determine whether incorporating such steps involved "an exercise of the inventive faculty." *Dann v. Johnston*, 425 U.S. 219, 225 (1976). Yet the Federal Circuit failed to implement this constitutionally grounded requirement. Prometheus's claims, which involve utterly conventional applications of unpatentable natural phenomena, scientific conclusions,

and mental processes, are not the work of an inventor.

The Federal Circuit also has erred twice in its analysis of the additional requirement that claims involving natural phenomena or abstract ideas not inappropriately preempt their use. *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 581 F.3d 1336 (Fed. Cir. 2009); *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347 (Fed. Cir. 2010). First, the court relied heavily on a transformation of matter analysis. While the transformation of matter test provides a "useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101," *Bilski*, 130 S. Ct. at 3227, it is inapposite for assessing the patentability of claims applying newly-discovered natural phenomena, which nearly always involve transformations of matter. Second, the court ignored the fact that the claims at issue preempt virtually all practical uses of the particular natural correlations they cover, holding them patentable under § 101 because they do not encompass correlations involving other drugs and diseases.

In sum, the Federal Circuit failed even to ask whether the claimed applications of natural phenomena reflect inventive activity, which they do not, and erred in applying this Court's preemption standard. The claims at issue do not meet either requirement and therefore are unpatentable.

ARGUMENT

I. Health Care Will Be Undermined If Conventional Medical Applications of Scientific Observations of Naturally-Occurring Bodily Processes Can Be Patented

The scope of patentable subject matter established by Congress in the Patent Act, 35 U.S.C. § 101, although quite broad, does not extend to scientific facts or observations of natural phenomena. *See Bilski,* 130 S. Ct. at 3225 (citing *Le Roy v. Tatham*, 55 U.S. 156 (1853)); *Diehr*, 450 U.S. at 185 (citing *Flook*, 437 U.S. at 593; and *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). The patents at issue here give Prometheus exclusive private ownership not of a new drug, a new diagnostic test, or even a new method of diagnosing a particular disease. Rather, the patents at issue effectively award Prometheus exclusive ownership of a pre-existing diagnostic test based on the mere *observation* of a naturally-occurring phenomenon: the correlation between the levels of certain metabolites produced naturally in the human body in response to administration of thiopurine drugs and the efficacy and toxicity of those drugs.

Amici medical associations recognize that health-care-related patents can enhance the provision of high-quality and cost-effective medical care. The financial incentive that patents offer supports the expensive and uncertain research required to identify, test, and gain approval for new pharmaceuticals, medical devices, diagnostic testing kits, and other products. In this respect, the patent system has

served patients and the medical profession well, drawing investment into the development of important new treatments.

Patents on scientific observations underlying medical care, however, do not have these salutary effects. Such patents erode the quality of patient care by limiting use of the very knowledge on which physicians must rely to diagnose and treat their patients, threaten to stifle innovation and the development of personalized medicine, and raise ethical concerns for physicians.

A. Patents on Scientific Observations Burden Physicians' Use of Pre-Existing Laboratory Tests and Erode Their Ability to Provide Quality Patient Care

A doctor who administers thiopurine drugs and tests metabolite levels infringes the claims at issue *merely by considering what to do about the results in light of relevant scientific information* about the correlation between dosage and efficacy or toxicity. This is the case even if he or she had a pre-existing practice of testing levels of the same metabolites and adjusting dosages of thiopurine drugs based on the test results.

The potential ramifications of the Federal Circuit's ruling that claims of this sort are patentable are profound and sobering. By uncovering a correlation between obesity and a particular illness, for

example, a researcher could obtain a patent on the process of having a patient step on a scale and then considering that natural correlation in deciding whether to recommend that the patient diet to lose weight. Any entity that made or sold scales and that dared to mention the correlation in a brochure might then be liable for intentionally inducing infringement. An observation that some patients tend to run a particularly high fever if given too much of a particular drug could lead to a patent on taking a patient's temperature and considering whether to raise or lower the dosage with that natural response in mind. Patients, physicians, and thermometer manufacturers might directly or indirectly infringe because a thermometer reading "indicates" that it might be advisable to adjust dosage of the drug. Such results are unthinkable, yet are eminently plausible applications of the Federal Circuit's analysis in this case.

There can be no design around a scientific fact. A physician who learns, from the medical literature, colleagues, continuing medical education, or elsewhere, of the natural correlation between metabolite levels and drug efficacy and toxicity cannot—and should not—put that knowledge out of mind. Quality patient care demands that a physician make treatment decisions in light of current medical knowledge. If natural correlations, such as those claimed here, are patented, physicians considering how to personalize their patients' care in light of the full and evolving scope of available scientific information will become mired in a thicket of exclusive rights. Not only might

a doctor infringe multiple patents by considering the results of a battery of diagnostic tests, but each test might be the subject of multiple, overlapping, patented guidelines.

In addition, if the claims at issue here were properly patentable, a laboratory such as Mayo might induce infringement simply by informing a doctor of the correlation in conjunction with delivery of test results or perhaps even by merely publishing articles or brochures discussing the correlation. Indeed, confronting very similar facts in *Metabolite Labs., Inc. v. Lab. Corp. of America Holdings*, 370 F.3d 1354 (Fed. Cir. 2004), the Federal Circuit found that the defendant laboratory had induced infringement through the publication of medical articles. *Id.* at 1365. To avoid inducement liability, laboratories would be forced to negotiate and pay license fees to multiple holders of such diagnostic correlation patents and might well decide to forego offering some tests. Moreover, patentees might decide to license their patents only to selected laboratories and physicians, restricting test availability and driving up costs.

If patent licenses are required for physicians merely to *consider* newly-discovered implications of well-established diagnostic tests and laboratories become indirect infringers merely by educating doctors about those implications, it is hard to imagine how quality patient care can result. Laboratories and physicians will expend time and resources tracking, interpreting, and licensing such patents, rather than

on improving patient care. Higher-priced medical care is the inevitable result.

B. Patents on Scientific Observations Threaten to Stifle Innovation, Including the Development of Personalized Medicine

Basic scientific facts are "part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none." *Bilski*, 130 S. Ct. at 3225 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). To promote medical innovation, basic facts, such as the relationship between levels of drug metabolites and the drug's efficacy and toxicity, must be freely accessible and widely disseminated. These patentees are neither the first nor the last to study the implications of these particular metabolite levels for human health. Physicians' understanding of the body's natural responses to treatment, such as the correlations involved here, accumulates over time through clinical practice and research, often leading to revisions of treatment guidelines and adaptation of those guidelines to reflect distinct recommendations for patients with particular illnesses or personal characteristics.

Patents are not needed to incentivize this study of clinical correlations and would stifle rather than incentivize developments in the practice of personalized medicine. The Secretary's Advisory Committee on Genetics, Health, and Society conducted an

extensive investigation into the need for patents in the closely-related context of genetic diagnostic testing and found:

> [P]atents do not appear to be necessary to stimulate research and genetic test development. . . . [S]cientists are principally motivated to conduct research by their curiosity, career ambitions, and desire to advance understanding of health and disease. . . . Similarly, laboratories have sufficient non-patent incentives to develop genetic tests: clinical need and demand drive development, and development costs are minimal.[2]

Patents are even less necessary to motivate academic researchers and clinicians to uncover correlations such as those claimed here. To improve existing treatment regimens, laboratories such as Mayo continually strive to develop more accurate standards for the clinical interpretation of metabolite levels. Researchers seek to study how these metabolite levels correlate with efficacy and toxicity in different clinical contexts and to develop appropriately tailored clinical approaches. The need for time-consuming, costly, and risky patent clearing and licensing, coupled with the possibility that patentees will simply refuse to license, will chill such research and raise its costs. Patent

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[2] SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, DEP'T OF HEALTH & HUMAN SERVS., GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS (2010) at 90, available at http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf (last visited Sept. 6, 2011).

claims such as those at issue here impermissibly burden medical research, effectively "shut[ting] the door" to scientific progress. *O'Reilly v. Morse*, 56 U.S. 62, 113 (1853).

C. Patents on Scientific Observations Raise Ethical Concerns for Physicians

Physicians have longstanding ethical obligations to advance and share useful medical knowledge with patients and other physicians. Principle V of the AMA's Principles of Medical Ethics states, "[a] physician shall continue to study, apply, and advance scientific knowledge," and "make relevant information available to patients, colleagues, and the public. . . ."[3] Opinion 9.095 of the Code of Medical Ethics of the AMA, reaffirmed in 2008, elaborates upon this basic principle:

> Physicians have ethical responsibilities not only to learn from but also, when possible, to contribute to the total store of scientific knowledge. Physicians should strive to advance medical science and make their achievements known through publication or other means of disseminating such information. This encourages physicians to innovate and to share ensuing advances. The use of patents, trade secrets, confidentiality

[3] Available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/principles-medical-ethics.shtml (last visited Sept. 6, 2011).

> agreements, or other means to limit the availability of medical procedures places significant limitation on the dissemination of medical knowledge, and is therefore unethical.[4]

Basic scientific observations that could be useful in reaching diagnoses and treating patients or in devising medical innovations are quintessential examples of the kinds of knowledge that physicians are obliged to share freely.[5]

Physicians also have ethical obligations to consider the most up-to-date scientific information available when treating their patients. Measurements and observations such as those at issue here are part of the broader clinical evaluation that physicians must undertake when treating patients. It is a routine part of the practice of medicine – indeed, it is essential to meet appropriate medical standards of care – for physicians to monitor metabolite levels and to use those levels along with other laboratory and clinical

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[4] Available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion9095.page# (last visited Sept. 6, 2011).

[5] *See* Opinion 9.08 ("Physicians have an obligation . . . to report the results of clinical and laboratory research. . . . The intentional withholding of new medical knowledge, skills, and techniques from colleagues for reasons of personal gain is detrimental to the medical profession and to society and is to be condemned."), available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion908.shtml (last visited Sept. 6, 2011).

parameters to guide dosage adjustments, thereby providing necessary and appropriate medical care for their patients. In sum, to interpret the patent laws so as to make scientific observations eligible for patent protection threatens to undermine, rather than promote, the ethical practice of medicine.

II. The Claims at Issue Are Conventional, Rather than Inventive, Applications of Natural Phenomena and Mental Steps and Hence Are Unpatentable

Prometheus's patent claims run afoul of the long-standing ban on patenting "laws of nature, physical phenomena, and abstract ideas." *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 309). While patents are available for inventive applications of natural phenomena and abstract ideas, they may not be granted for merely conventional applications. *Bilski*, 130 S. Ct. at 3230 (quoting *Flook*, 437 U.S. at 590).

The claims at issue consist at most of the following steps: (a) administering a thiopurine drug that is broken down by the body into a particular metabolite (6-TG or 6-MMP); and (b) determining the level of the metabolite, "wherein" metabolite levels above or below certain specified levels provide "a warning that an adjustment in dosage may be required." *Prometheus*, 628 F.3d at 1351 (quoting *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04-CV-1200,

2008 WL 878910 at *1 (S.D. Cal. Mar. 28, 2008) (hereinafter "Dist. Ct. Op.").

Long before the patentee drafted his claims, physicians treating autoimmune disorders administered thiopurine drugs, measured their patients' resulting levels of 6-TG and 6-MMP metabolites, and recognized the relationship between metabolite levels and optimal dosage. The patentee's only contribution is encapsulated in the "wherein" clauses: he analyzed statistical correlations between the metabolite levels and the therapeutic efficacy and toxicity of the drugs, and inferred dosage adjustment guidelines from those studies. U.S. Patent No. 6,355,523 col.8 ll.43-46 (filed Apr. 8, 1999) ("the '523 Patent"); U.S. Patent No. 6,680,302 col.8 ll.48-51 (filed Dec. 27, 2001) ("the '302 Patent"). The "wherein" clauses merely report these unpatentable scientific conclusions, which are based on observations of unpatentable natural phenomena. To the extent the "wherein" clauses require anything from physicians, they require only the unpatentable abstract mental state of being "warned."

The Federal Circuit found that the claims as a whole were patentable only because the patentee included the steps of "determining" the metabolite levels and, in some claims, "administering" the drugs. *Prometheus*, 628 F.3d at 1355. However, the incorporation of these utterly conventional steps does not meet the constitutionally grounded requirement that a patentee be an *inventor* of a patentable application of a newly-discovered law of nature, physical phenomenon or abstract idea, rather than merely a

competent draftsman of claims covering entirely conventional applications of the phenomenon or idea.

A. Constitutionally Grounded Precedent Requires that Patentable Applications of Natural Phenomena and Mental Steps Reflect Inventive Activity

1. One Who Applies a Natural Phenomenon or Abstract Idea in a Conventional Manner Is Not an Inventor

The Constitution grants Congress the power "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const., art. I, § 8, cl. 8. The limitations of this grant have long informed this Court's interpretation of the patent statutes. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 6 (1966) ("Innovation, advancement, and things which add to the sum of useful knowledge are inherent requisites in a patent system which by constitutional command must 'promote the Progress of . . . useful Arts.' This is the *standard* expressed in the Constitution and it may not be ignored.") (emphasis in original).

A patent may be awarded only to an *inventor of an application* of a natural phenomenon or abstract idea. *See, e.g., Le Roy*, 55 U.S. at 175 ("The elements of the power exist; the invention is not in discovering them, but in applying them to useful objects."); *MacKay Radio Co. v. Radio Corp. Am.*, 306 U.S. 86, 94

(1939) ("While a scientific truth, or the mathematical expression of it, is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be."); *Dann*, 425 U.S. at 225 ("Invention – *i.e.*, an exercise of the inventive faculty . . . has long been regarded as an absolute prerequisite to patentability.") (internal quotation marks omitted); *cf. Feist Publ'ns, Inc. v. Rural Tel. Serv. Co.*, 499 U.S. 340, 346 (1991) (interpreting U.S. Const. art. I, § 8, cl. 8, to permit copyright protection only for "Authors").

Neither the mere application of "skill," *Funk Bros.*, 333 U.S. at 132, nor the addition of "conventional or obvious" activity, *Bilski,* 130 S. Ct. at 3230 (quoting *Flook*, 437 U.S. at 590), nor competent claim drafting, *Flook*, 437 U.S. at 590, is sufficient to transform the discoverer of a natural phenomenon or scientific principle into an inventor of a patentable application of that principle. To be eligible for a patent, the applicant must invent and claim an *application* of the natural phenomenon or abstract idea that reflects human ingenuity and is not wholly conventional. *Bilski*, 130 S. Ct. at 3230 (quoting *Flook*, 437 U.S. at 590, 594); *Flook*, 437 U.S. at 593-95; *Funk Bros.*, 333 U.S. at 132; *see also Chakrabarty*, 447 U.S. at 309-10, (holding patentable a nonnaturally occurring composition of matter deemed "a product of human ingenuity having a distinctive name, character and use" (quotations omitted)).

In *Funk Bros.*, decided shortly before the enactment of the 1952 Patent Act, this Court considered a

claim to an "inoculant" made up of a combination of natural bacterial strains that assist plants in nitrogen-fixing by forming nodules on their roots. 333 U.S. at 130. Though a variety of such bacteria had been identified, they were used and sold separately because they inhibited one another's activity. The patentee "discovered" the scientific fact "that there are strains of each species of root-nodule bacteria which do not exert a mutually inhibitive effect on each other," *id.*, and claimed an inoculant combining mutually-non-inhibitive species. Despite the fact that the inventor had "made a new and different composition of non-inhibitive strains which contributed utility and economy to the manufacture and distribution of commercial inoculants," this Court deemed the claim unpatentable:

> [H]owever ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants. . . . [O]nce nature's secret of the non-inhibitive quality of certain strains of the species of [bacteria] was discovered, the state of the art made the production of a mixed inoculant a simple step. Even though it may have been the product of skill, it was not the product of invention.

Id. at 131. Though the patentee was the discoverer of a natural phenomenon, he was not the inventor of a patentable application of that phenomenon.

The requirement that a patentee be an *inventor* of an application of a law of nature, physical phenomenon, or abstract idea did not disappear when Congress enacted the 1952 Patent Act. Thus, for example, in *Parker v. Flook* the applicant had claimed a "Method for Updating Alarm Limits" during catalytic conversion, which employed a formula. *Flook*, 437 U.S. at 585. This Court assumed, for purposes of analysis, that the formula was "novel and useful and that [the applicant] discovered it." *Id.* at 588. After posing the question "whether the discovery of this feature makes an otherwise conventional method eligible for patent protection," *id.*, the Court concluded:

> The notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process exalts form over substance. A competent draftsman could attach some form of post-solution activity to almost any mathematical formula; the Pythagorean theorem would not have been patentable, or partially patentable, because a patent application contained a final step indicating that the formula, when solved, could be usefully applied to existing surveying techniques.

Id. at 590. The presumed originality of Flook's formula did not make him an inventor. "Whether the algorithm was in fact known or unknown at the time of the claimed invention, as one of the 'basic tools of scientific and technological work,' it is treated as though it were a familiar part of the prior art." *Id.* at 591 (quoting *Benson*, 409 U.S. at 67).

In *Chakrabarty*, on the other hand, this Court affirmed the patentability of a "man-made" genetically engineered bacterium, because the claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity." *Chakrabarty*, 447 U.S. at 309. The Chakrabarty bacterium was "not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101." *Id.* at 310. Having applied "human ingenuity" to invent a nonnaturally occurring bacterium, Chakrabarty was eligible for patent protection (assuming he could meet the other requirements of the Patent Act). *Id.* at 310.

Diehr did not change this fundamental requirement. There, this Court considered a patent claim to a "process for molding raw, uncured synthetic rubber into cured precision products," which employed the Arrhenius equation. *Diehr*, 450 U.S. at 177. Unlike *Funk Bros.*, *Flook*, and the present case, *Diehr* did not concern an applicant who claimed to have discovered a new natural phenomenon or devised a new formula. The applicant did not (and could not) claim to have invented the Arrhenius equation, which, among its many uses, had "long been used to calculate the cure time in rubber-molding presses." *Id.* at 178, n.2. The issue in *Diehr* was whether the *mere inclusion* of a formula rendered the applicant's claims to an industrial rubber molding process unpatentable. This Court rejected an approach that would "dissect the claims into old and new elements and then [] ignore the presence of the old elements in the analysis,"

confirming the longstanding rule that combinations that include unpatentable elements may constitute patentable inventions. *Id.* at 188. Because the Arrhenius equation was a well-established part of the prior art, which would contribute to the evaluation of nonobviousness under 35 U.S.C. § 103, the Court did not confront the central issue in the present case, which involves an allegedly new scientific observation.

Where, as in *Funk Bros.*, *Flook*, and the present case, patent claims call out a purportedly new natural phenomenon or abstract idea, the requirement that patents issue only to "Inventors," U.S. Const. art. I, § 8, cl. 8, constrains patentability under Section 101. Claim limitations that do no more than apply a natural phenomenon or abstract idea in a conventional way are "insignificant," *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 191-92), because the claim "as a whole," *Diehr*, 450 U.S. at 188, does not reflect inventive activity. A patent may not be granted for a scientific discovery simply because the discoverer is a "competent draftsman." *Flook*, 437 U.S. at 590.

2. The Inventor Requirement Must Be Enforced Under Section 101 and Is Not Wholly Subsumed by Section 103's Nonobviousness Requirement

The nonobviousness requirement, 35 U.S.C. § 103, "comports with [] constitutional strictures," by ensuring that patents issue only for claims that are sufficiently inventive in comparison to "the prior art."

Graham, 383 U.S. at 10-12, 16. "The prior art," as defined by 35 U.S.C. § 102,[6] encompasses only "art" previously known, used, published, or invented by human beings. Section 103's nonobviousness analysis therefore cannot subsume the inventor requirement where, as here, a patentee claims to have discovered natural phenomena or devised abstract ideas. In such cases, the inquiry into whether the patentee is an inventor properly takes place under the auspices of Section 101. *See Flook*, 437 U.S. at 590; *Chakrabarty*, 447 U.S. at 310.

B. Prometheus's Claims Are Unpatentable Conventional Applications of Natural Phenomena and Do Not Reflect Inventive Activity

1. Correlations Between Metabolite Levels and Drug Efficacy and Toxicity Are Unpatentable Natural Phenomena

The Federal Circuit did not disturb the District Court's correct findings (1) that the observed correlations between metabolite levels and drug toxicity "were natural phenomena, not patent-eligible inventions because the correlations resulted from a natural

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[6] *See* DONALD S. CHISUM, CHISUM ON PATENTS § 5.03[3], ("Section 103 does not expressly define what sources might be looked to as 'prior art' to determine obviousness. However, the opening phrase clearly implies that the provisions of Section 102 are to be the guide.").

body process," (2) that the patentee "did not 'invent' the claimed correlation; rather '6-TG and 6-MMP are products of the natural metabolizing of thiopurine drugs,'" and (3) that the patentee "'merely observed the relationship between these naturally produced metabolites and therapeutic efficacy and toxicity.'" *Prometheus*, 628 F.3d at 1352 (quoting Dist. Ct. Op. at *7). It is true, of course, that the metabolites are produced when the body reacts to human administration of a drug. But the body's reaction is a natural phenomenon nonetheless. In patent law, "natural" means "nature's handiwork" as generally juxtaposed with the products of human agency and ingenuity. *See Chakrabarty*, 447 U.S. at 310; *Flook*, 437 U.S. at 591-94.

In *Funk Brothers*, for example, the newly-discovered mutual non-inhibition of the bacterial strains was a natural phenomenon even though they displayed that property when combined by human action into an inoculant. *Funk Bros.*, 333 U.S. at 131 (the bacteria "act[ed] quite independently of any effort of the patentee").

Similarly, this Court, in discussing the English case, *Neilson v. Harford*, 151 Eng. Rep. 1266 (1841), distinguished between the unpatentable "principle that hot air will promote the ignition of fuel better than cold" and the patentable invention of a mechanical apparatus for supplying hot air to a furnace. *O'Reilly*, 56 U.S. at 114-16. The fact that burning fuel in a furnace is a human activity did not render the fuel's natural response to a supply of hot air

patentable. Nor did the fact that printing characters at a distance is a human endeavor save Morse's claim to the basic scientific concept of using "the motive power of the electric or galvanic current" to make such characters. *Id.* at 119. Conversely, Bell's claim to the use of undulatory current for transmitting speech was patentable because it was "not for the use of a current of electricity *in its natural state as it comes from the battery. . . .*" *Dolbear v. American Tel. Cases*, 126 U.S. 1, 534 (1888) (emphasis added). Clearly, the electricity flow produced by a battery occurs only because of human activity, yet this Court rightly deemed that flow "natural."

To comport with longstanding case law, a phenomenon must be deemed natural when it proceeds without direct human agency, even if in response to a human stimulus. Indeed, Prometheus's own expert displayed this understanding, testifying that "the key therapeutic aspect of such thiopurine drugs is that they are converted naturally by enzymes within the patient's body to form an agent that is therapeutically active." Dist. Ct. Op. at *7. Any other understanding of "natural phenomenon" would lead to absurd results: the process of digestion would be non-natural when digesting synthetic foods and natural when digesting wild berries, the process of sunburning would be non-natural when it occurred in tanning booths and natural when it happened on a beach, and so forth.

The Federal Circuit rightly concluded that Prometheus's claims involve "naturally occurring correlations

between metabolite levels and efficacy or toxicity." *Prometheus*, 628 F.3d at 1355.

2. The Claimed Metabolite Levels at Which Physicians Should Consider Revising Dosage Are Unpatentable Scientific Conclusions

The claimed metabolite levels at which physicians should consider raising or lowering dosage are unpatentable scientific conclusions. To arrive at the claimed levels, the patentee analyzed clinical data concerning the responses of a group of patients with inflammatory bowel disease to the administration of thiopurine drugs. *See* '302 Patent at cols.16-20; '623 Patent at cols.16-20. He observed, for example, that in a group of 93 pediatric patients with inflammatory bowel disease, 78% of those with 6-TG levels above 230 pmol/$8x10^8$ red blood cells responded well to the drug, while only about 40% of those with levels below that value responded well. '302 Patent at col.17 l.26-col.18 l.54, fig. 3; '623 Patent at col.17 l.26-col.18 l.54, fig. 3. He then used statistical methods to infer from such observations the claimed guideline of 230 pmol/$8x10^8$ red blood cells for increasing drug dosage. *See, e.g.*, '302 Patent, claim 1; '623 Patent, claim 1. Similarly, the patentee inferred a guideline for decreasing dosage from observations of patients who experienced toxic reactions to the drugs.

Such guidelines are merely scientific conclusions based on observing the underlying natural phenomena. This Court recognized long ago that "a scientific

truth, or the mathematical expression of it, is not a patentable invention." *MacKay Radio*, 306 U.S. at 94.

3. The "Wherein" Clauses Cover Mere Thought About Natural Phenomena and Scientific Conclusions

The final "wherein" clauses of the claims at issue rely on the unpatentable metabolite level guidelines inferred from observing the natural correlations between metabolite levels and efficacy and toxicity to "indicate a need" to adjust dosage. *Prometheus*, 628 F.3d at 1350. The claim language "indicates a need" was construed to mean only that the test results provide "'a warning that an adjustment in dosage may be required.'" *Id.* at 1351 (quoting Dist. Ct. Op. at *1). Notably, "[t]his construction did not require doctors to adjust drug dosage if the metabolite level reached the specified levels; rather, the court found the two 'wherein' phrases to mean 'that when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required, if the doctor believes that is the proper procedure.'" *Id.*

The "wherein" clauses thus do not require any volitional action by physicians beyond reviewing the results of a test. A doctor who merely orders a measurement of a patient's metabolite levels, reviews the results, and is aware of the relationships among metabolite levels and efficacy and toxicity reflected in the claims is an infringer. The Federal Circuit

correctly "agree[d] with the district court that the final 'wherein' clauses are mental steps and thus not patent-eligible per se." *Id.*

4. The Claims as a Whole Are Unpatentable Conventional Applications of the Observed Natural Correlations

In this case, the patentee administered a conventional drug, performed conventional tests to measure a natural bodily response to the drug, analyzed and interpreted the data, and suggested that physicians should think about the results when treating their patients. The claims at issue reflect nothing more. There is nothing unconventional in the "administering" and "determining" limitations of the claim. Nor is the combination of elements as a whole anything but conventional medical application of the observed natural correlations. The Federal Circuit thus erred in holding that these limitations transformed unpatentable natural phenomena and abstract ideas into patentable subject matter. *Prometheus*, 628 F.3d at 1355-56. While the Federal Circuit gave lip service to the importance of "the critical question, 'What did the applicant invent?'," it never seriously addressed this fundamental issue. *Id.* at 1359.

Enforcement of the requirement that a patentee *invent an application* of any natural phenomenon or abstract idea incorporated in a claim is critical for innovation in medicine and other fields dependent on scientific advances. Moreover, when, as here, courts

ignore this requirement, patentees have incentives to engage in gamesmanship in claim drafting. As Judge Rader very recently emphasized, "[w]hen careful claim drafting or new claim formats avoid eligibility restrictions, [patentable subject matter] doctrine becomes very hollow." *Classen Immunotherapies, Inc. v. Biogen IDEC*, 2011 WL 3835409 at *16 (Fed. Cir. Aug. 31, 2011) (Rader, J., additional views).

While he correctly diagnoses the problem, Judge Rader's conclusion that courts should "decline to accept invitations to restrict subject matter eligibility" sweeps too broadly. *Id.* at *15. In *Classen*, for example, the Federal Circuit held that the unpatentable observation that one immunization schedule results in fewer side effects than another became patentable subject matter when the conventional step of following the less risky schedule was added to the claims. *Id.* at *10 (majority opinion). As Judge Moore emphasized in dissent, "Classen's claims readily illustrate that linking a natural phenomenon or abstract idea to a useful or practical result is no barrier for a competent patent drafter attempting to monopolize unpatentable subject matter." *Id.* at *23 (Moore, J., dissenting).

Enforcing the requirement of inventive activity, on the other hand, would address such attempts to draft around the ban on patenting natural phenomena and abstract ideas. In the present case, the question of whether Prometheus's claims reflect "an exercise of the inventive faculty," *Dann*, 425 U.S. at 225, is easily answered: the patentee in this case is a physician, a

medical researcher, and a competent claim draftsman, but not, as least with regard to the claims at issue here, an inventor. The claims are therefore unpatentable under § 101.

III. The Federal Circuit Also Erred in its Transformation of Matter and Preemption Analyses

The Federal Circuit's patentable subject matter analysis focused on the requirement that patent claims not be overly preemptive of uses of natural phenomena and abstract ideas. *Prometheus*, 628 F.3d at 1355. The court concluded that the addition of the "administering" and "determining" steps met this requirement because those steps rendered the claims "sufficiently definite to confine the patent monopoly to within rather definite bounds," *id.* at 1357, involved a "transformation of matter," *id.* at 1355-56, and did not constitute "insignificant extra-solution activity." *Id.* at 1357-58. The Federal Circuit's heavy reliance on the transformation of matter test is misplaced, however, because that test is inapposite to claims based on natural phenomena. The court's preemption analysis, moreover, failed to focus on the particular correlations recited in the claims and therefore did not recognize the substantial burden that the claims place on downstream research.

A. The Transformation of Matter Test Is Inapposite to Natural-Phenomenon-Based Claims

Both before and after the remand for reconsideration in light of this Court's opinion in *Bilski*, the Federal Circuit focused the bulk of its attention in this case on applying the transformation of matter test. *Prometheus*, 628 F.3d at 1355-56; *Prometheus*, 581 F.3d at 1345-46. As this Court held in *Bilski*, that test is "a useful and important clue, an investigative tool, for determining whether *some* claimed inventions are processes under § 101." 130 S. Ct. at 3227 (emphasis added).

The machine or transformation test is inapposite, however, to determining whether a claim preempts a natural phenomenon. Photosynthesis, the freezing of water into ice and its evaporation into steam, and the rusting of iron – all involve transformations of matter, but are unpatentable unless they are part of an inventive application of the phenomenon. Similarly, the measurement or use of a natural phenomenon will ordinarily involve a physical transformation. As Justice Breyer explained in his dissent to dismissal of *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, "to use virtually any natural phenomenon for virtually any useful purpose could well involve the use of empirical information obtained through an unpatented means that might have involved transforming matter." 548 U.S. 124, 136 (2006) (Breyer, J., dissenting). Whatever the usefulness of the transformation of matter test in determining the patentability of processes

similar to the abstract hedging methods in *Bilski*, 130 S. Ct. at 3227-28, the fact that a natural phenomenon, or a method of observing or measuring the phenomenon, involves a transformation of matter has little bearing on whether a patent claim preempts that phenomenon.

Moreover, the transformation of matter test is highly manipulable in cases involving scientific observations of natural phenomena. Where, as here, the claim simply requires "determining" the level of a natural phenomenon, the outcome may depend on whether the court chooses to infer that the measurement requires a transformation of matter. Thus, in *In re Grams*, 888 F.2d 835 (Fed. Cir. 1989), the Federal Circuit determined that a claim step requiring "performing . . . clinical laboratory tests," *id.* at 836, was unpatentable because it "did not require the performing of clinical tests on individuals that were transformative . . . because the tests were just to 'obtain data.'" *Prometheus*, 628 F.3d at 1358 (explaining *Grams*). In *Prometheus*, however, the court assumed that the "determining" step of the claims involved "[s]ome form of manipulation . . . or some other modification of the substances to be measured [] to extract the metabolites from a bodily sample and determine their concentration," *Prometheus*, 628 F.3d at 1357, and, as a result, concluded that Prometheus's claims were patentable. *Id.*

The Federal Circuit's attempt to distinguish the claims at issue here from those in *Grams* based on the extent to which the claims involve transformations of

matter makes little sense because the transformation of matter test is simply inapposite to the real issues at hand – whether the claims apply a natural phenomenon to make a patentable contribution to the "useful Arts" and whether they improperly preempt downstream uses of the phenomenon.

B. The Federal Circuit Failed to Recognize that the Claims at Issue Preempt Virtually All Practical Uses of the Covered Correlations

The Federal Circuit's analysis of the preemption issue stumbles at the outset by focusing on whether the claims "wholly preempt all uses of the recited correlations." *See Prometheus*, 628 F.3d at 1355. This Court's precedents do not demand that claims "wholly preempt all uses" of a natural phenomenon or abstract idea to be unpatentable. *See Bilski*, 130 S. Ct. at 3230 ("the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment' or adding 'insignificant postsolution activity'") (quoting *Diehr*, 450 U.S. at 191-92); *Flook*, 437 U.S. at 589-90 (claims were unpatentable under § 101 even though applicant "does not seek to 'wholly preempt the mathematical formula'") (quoting *Benson*, 409 U.S. at 71-72).

Moreover, the Federal Circuit erred by failing to focus its inquiry on preemption of uses of the *correlations recited in the claims*. The court reasoned that:

> [T]he claims recite specific treatment steps, not just the correlations themselves. And the steps involve a particular application of the natural correlations: the treatment of a specific disease by administering specific drugs and measuring specific metabolites. As such . . . the claims do not preempt all uses of the natural correlations; they utilize them in a series of specific steps. . . . The [claims'] inventive nature stems not from preemption of all use of these natural processes, but from the application of a natural phenomenon in a series of steps comprising particular methods of treatment. Other drugs might be administered to optimize the therapeutic efficacy of the claimed treatment.

Prometheus, 628 F.3d at 1355. This reasoning simply does not address whether the claims preempt "the recited correlations," even though it may purport to do so. *Id.* The claims recite no "specific treatment steps" other than the administration of the drug that triggers the body's creation of the metabolites and the measurements necessary to observe those correlations. There can be few, if any, practical uses of the "recited correlations" that would not be preempted by these claims.

In the end, the Federal Circuit appears to be convinced that the claims are not preemptive solely because they are confined to administering one of a specific group of drugs and measuring one of a specific group of metabolites and are thus "sufficiently

definite to confine the patent monopoly to within rather definite bounds." *Prometheus*, 628 F.3d at 1357.

This conclusion is incorrect. Though two particular metabolites are specified in the claims, the claims cover all autoimmune disorders in all contexts. Because of this broad coverage, the claims preempt a wide swath of scientific study of responses to treatment for different diseases. As an example, Prometheus contended that dermatologist Dr. el-Azhary infringed the patents while studying autoimmune disorders far removed from the inflammatory bowel disease studies from which the claims were derived, Brief for Petitioners at 11-13, and for which she eventually discovered efficacy ranges for the measured metabolites quite different from those in the patent claims.[7] Even a claim limited to a specific disease, however, significantly preempts research into whether treatment of that disease should be personalized based on individual patient characteristics, such as age or gender, or on the results of complementary tests. The Federal Circuit's preemption analysis simply ignored these downstream effects.

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[7] Rokea A. el-Azhary, *et al.*, *Thioguanine Nucleotides and Thiopurine Methyltransferase in Immunobullous Diseases: Optimal Levels as Adjunctive Tools for Azathioprine Monitoring*, 145 ARCH. DERMATOL. 644 (June 2009).

CONCLUSION

For the foregoing reasons, this Court should clarify that patents may issue only for applications of natural phenomena and abstract ideas that reflect use of the "inventive faculty" and are not merely conventional and that the transformation of matter test is inapposite to the patentable subject matter analysis for claims directed at natural phenomena and scientific conclusions. Because the claims at issue are unpatentable under 35 U.S.C. § 101, the Federal Circuit's ruling in this case should be reversed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-1150

IN THE
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES),
and MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF *AMICUS CURIAE* AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF RESPONDENT

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STATEMENT OF INTEREST

The American Intellectual Property Law Association ("AIPLA") submits this brief as amicus curiae in support of Respondent, Prometheus Laboratories, Inc. ("Prometheus").[1] AIPLA is a national bar association whose approximately 16,000 members have interests and practice primarily in the areas of intellectual property. AIPLA's members include attorneys in private practice, corporate practice, and government or academic positions involved directly or indirectly in the practice of patent, trademark, copyright, unfair competition, and other fields of law affecting intellectual property. AIPLA members include both owners and users of intellectual property, representing the interests of both plaintiffs and defendants. The issue of patent eligible subject matter is vital to most, if not all, of AIPLA's members.

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[1] In accordance with Supreme Court Rule 37.6, amicus curiae states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the amicus curiae or its counsel. After reasonable investigation, AIPLA believes that (i) no member of its Board or Amicus Committee who voted to file this brief, or any attorney in the law firm or corporation of such a member, represents a party to this litigation in this matter, (ii) no representative of any party to this litigation participated in the authorship of this brief, and (iii) no one other than AIPLA, or its members who authored this brief and their law firms or employers, made a monetary contribution to the preparation or submission of this brief.

Many members of AIPLA practice in the biotechnology, pharmaceutical, and medical services industries. The Court's decision in this case will potentially impact thousands of issued patents and pending applications relevant to those industries. Although AIPLA has no interest in any party to this litigation or stake in the outcome of this case, it has an interest in seeking a correct and consistent interpretation of laws affecting intellectual property in general and in seeking a reaffirmance of the Court's precedent of giving a wide scope to the terms of 35 U.S.C. § 101.[2]

SUMMARY OF ARGUMENT

Section 101 of the patent statute identifies the classes of invention that are eligible for patent protection. That statute has been construed broadly by this Court to exclude only three categories of invention: laws of nature, physical phenomena, and abstract ideas. The diagnostic methods claimed by Prometheus do not fall into any of these excluded categories. Prometheus's methods, like many other patents directed to personalized medicine, therapeutic treatment of humans, and diagnostic methods, utilize the natural metabolic process of the human body, but those natural processes are not what is "claimed" and therefore should not serve as a

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[2] In accordance with Supreme Court Rule 37.3(a), the parties to this litigation have consented to the filing of this brief. The written consent of all parties has been entered in the docket of this case.

basis to deny patent protection. Simply put, the mere involvement of a natural metabolic process in claims directed to personalized medicine, therapeutic treatment of humans, or diagnostic methods should not be used as a basis to deny patent protection to that whole class of inventions, especially where the U.S. Patent and Trademark Office ("PTO") has been granting patents on these types of inventions for decades and where the patent statute explicitly recognizes them.

Most of Petitioners' complaints about Prometheus's patent claims are misdirected at patent eligibility under 35 U.S.C. § 101, and instead should be addressed to other provisions of the patent statute. For example, Petitioners' concerns that diagnostic method claims might stifle the medical community are already addressed by 35 U.S.C. § 287(c)(1), which exempts medical practitioners and related health care entities performing certain medical activities from being sued for patent infringement. Similarly, Petitioners' criticisms regarding the over breadth of Prometheus's claims are addressed by 35 U.S.C. §§ 102 (concerning the requirement of novelty), 103 (concerning the requirement of non-obviousness), and 112 (concerning the written description requirement). Moreover, in the recently enacted America Invents Act, Congress directed the PTO to conduct a study of the impact of limited uses of certain diagnostic method patents, necessarily showing that Congress recognizes diagnostic method patents as patent eligible subject matter under current law.

Therefore, this Court should conclude that Prometheus's claims are patent eligible under section 101 of the patent statute.

ARGUMENT

I. The Patent Statute Accounts for the Policy Concerns Raised by Mayo.

Petitioners raises a host of policy concerns in an attempt to convince this Court that the diagnostic claims in this case should not be eligible for patent protection under 35 U.S.C. § 101. The flaw in Petitioners' arguments, however, is that Congress has already balanced the competing policy concerns associated with diagnostic method claims and enacted specific provisions to address those concerns. And rather than amend section 101 of the patent statute, Congress enacted other provisions to take those concerns into account.

A. The Patent Statute Expressly Precludes Patent Infringement Lawsuits Against "Medical Practitioners."

In its brief, Mayo complains that diagnostic method patent claims

> prevent "doctors from using their best medical judgment," "force doctors to spend unnecessary time and energy to enter into license agreements," "divert resources from the medical task of health care to the legal

> task of searching patent files for similar simple correlations," and "raise the cost of health care while inhibiting its effective delivery."

Mayo Br. at 2 (quoting *Lab. Corp. of Am. Holdings v. Metabolite Labs.*, 548 U.S. 124, 138 (2006) (Breyer, J., dissenting from dismissal of petition for writ of certiorari) (hereinafter "*LabCorp*"). The patent statute, however, expressly precludes patent infringement lawsuits against medical doctors and the health care institutions with which they affiliate for performing certain medical activities, thereby negating these concerns.

The patent statute gives a patent holder the right to sue for patent infringement: "A patentee shall have remedy by civil action for infringement of his patent." 35 U.S.C. § 281 (2006). Section 287(c)(1), in turn, negates that right insofar as the suit would be with respect to "a medical practitioner's performance of a medical activity." 35 U.S.C. § 287(c)(1) (2006). More specifically, that section states that the "provisions of section[] 281 . . . shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity." *Id.* Thus, a patentee is not free to assert its patent against a medical practitioner for performing certain medical

activities.[3] The statute further explains that "'medical practitioner' means any natural person who is licensed by the State to provide the medical activity," that "'medical activity' means the performance of a medical or surgical procedure on a body," and that "'related health care entity' shall mean an entity with which a medical practitioner has a professional affiliation under which the medical practitioner performs the medical activity, including but not limited to a nursing home, hospital, university, medical school, health maintenance organization, group medical practice, or a medical clinic." *Id.* at § 287(c)(2).[4]

Therefore, Mayo's concerns regarding doctors being required to search patent files or obtain patent licenses are illusory. Furthermore, these provisions of section 287(c), providing relief from infringement for certain activities by medical practitioners, would not be necessary (and in fact would be meaningless)

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[3] Medical activity that is not covered by 35 U.S.C. § 287(c) includes, for example "the practice of a process in violation of a biotechnology patent." 35 U.S.C. § 287(c)(2)(A)(iii).

[4] Prometheus's patent claims are a "medical activity" within in the meaning of section 287(c)(2) because the claims require "administering a drug" to a patient and "determining the level" of a certain hormone in the patient. U.S. Patent No. 6,355,623, col. 20, ll. 13-16. *See generally Emtel, Inc. v. LipidLabs, Inc.*, 583 F. Supp. 2d 811, 819-24 (S.D. Tex. 2008) (holding that a claim directed to "diagnosing a medical condition," falls within the scope of 35 U.S.C. § 287(c)(2)).

if these types of activities were not otherwise considered eligible for patenting under section 101.

B. The Recently-Enacted America Invents Act Reflects the Careful Balance Struck by Congress in Connection with Patent Eligibility and Diagnostic-Method Claims.

On September 16, 2011, the President signed the Leahy-Smith America Invents Act (hereinafter referred to as the "America Invents Act" or "AIA"). Pub. L. No. 112-29, 125 Stat. 284 (2011). As stated in House Report No. 112-98, the AIA was "a 6-year work in progress," after numerous hearings before multiple committees of the Senate and House of Representatives. H.R. Rep. No. 112-98, at 57 (2011). In the AIA, Congress amended many provisions of the patent statute, but notably Congress declined to amend section 101, even though the process included numerous occasions for it to consider policy issues concerning patentable subject matter.

For example, in the AIA Congress affirmatively considered certain diagnostic method claims. *See id.* at § 27, 125 Stat. at 338-39. Rather than determine that such claims are not patent eligible, Congress simply required that the Under Secretary of Commerce for Intellectual Property and Director of the U.S. Patent and Trademark Office, referred to as "Director" in the patent statute, 35 U.S.C. § 3(a)(1) (2006), "conduct a study on effective ways to provide independent, *confirming* genetic

diagnostic test activity where gene patents *and exclusive licensing* for primary genetic diagnostic tests exist." AIA § 27(a), 125 Stat. at 338 (emphasis added). Thus, Congress explicitly recognized the existence of gene patents, and by referencing "exclusive licensing" for genetic diagnostic tests, Congress implicitly recognized the eligibility for patent protection of diagnostic method claims generally. . In the AIA, Congress merely requested a study only of a particular use of such tests to provide "second opinion[s]" to the results first obtained using a patented test. *Id.* at § 27(b)(2).

Elsewhere in the AIA, Congress did more than simply direct a study on certain patentable subject matter. For example, the new law directs that "no patent may issue on a claim directed to or encompassing a human organism." AIA § 33(a), 125 Stat. at 340. Likewise, Congress directed that claims directed to "any strategy for reducing, avoiding, or deferring tax liability" shall be "deemed insufficient to differentiate a claimed invention from the prior art." AIA § 14(a), 125 Stat. at 327. Although not couched in terms of patent eligibility, the effect of that provision is to preclude patent eligibility for tax strategies because the patent statute otherwise excludes patent protection for inventions in the prior art. 35 U.S.C. § 102 (2006), *amended by* AIA § 3, 125 Stat. at 285-87.

Thus, in considering the AIA, Congress demonstrated its purview over the patentable subject matter issues that Petitioners raise.

Congress in that legislation affirmatively excluded certain types of inventions from patent eligibility, but it did not exclude patent protection for diagnostic method inventions. In connection with diagnostic method inventions, the balance struck by Congress at this time is only that a study of a limited subset of such inventions be conducted by the Director. In light of that balance, it would be inappropriate for this Court to conclude otherwise in this case. *See generally Bilski v. Kappos*, 130 S. Ct. 3218, 3228 (2010) ("A conclusion that business methods are not patentable in any circumstances would render § 273 [of title 35] meaningless. This would violate the canon against interpreting any statutory provision in a manner that would render another provision superfluous.").

II. Prometheus's Method Claims Are Patent Eligible under Section 101 and This Court's Precedent.

A. The Methods Claimed By Prometheus Are Not Laws of Nature or Physical Phenomena.

Claim 1 of Prometheus's U.S. Patent No. 6,355,623 recites two physical steps: (1) administering a certain type of drug to a patient, and (2) determining the extent to which that patient metabolized the drug into a specific metabolite. U.S. Patent No. 6,355,623, col. 20, ll. 13-17. Neither of these steps is a "law of nature." Neither of these steps is a natural "physical phenomenon." Ignoring these steps might allow one to focus exclusively on

that portion of the claim directed to a "need to increase" or a "need to decrease" the amount of drug later administered to that patient. However, such analysis would be inappropriate and conflict with this Court's statement in *Diamond v. Diehr*:

> In determining the eligibility of respondents' claimed process for patent protection under § 101, their claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made. The "novelty" of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter.

450 U.S. 175, 188-89 (1981).

Viewing the claim as a whole, as this Court directs we must, the claim recites a patent eligible "process," 35 U.S.C. § 101 (2006), and that process is not a law of nature, a physical phenomenon, or an abstract idea. *See Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). Prometheus's claims require administering a drug to a patient and measuring

that patient's ability to transform the drug into its metabolite. Both of these steps are the result of human intervention and do not occur in nature. The "wherein" clauses of the claims which follow these steps *apply* the results of these man-made steps to allow a determination whether an adjustment in the treatment is necessary. The distinction between a claim to a mere principle and a claim to a process which applies the principle to effect a useful result, has long been recognized by the Court. *See, e.g., Tilghman v. Proctor*, 102 U.S. 707, 724 (1880).

To be sure, Prometheus's patent claims, like many other patent claims related to the therapeutic treatment of humans, rely on the natural metabolic processes of the human body (much like many mechanical devices rely on the natural process of gravity). The mere fact that an invention exploits natural metabolic processes, however, cannot be used as a basis to render this whole class of inventions ineligible for patent protection. Over a long line of cases, this Court has explained that abstract ideas, laws of nature, and natural phenomena are not eligible for patent protection under § 101, but a practical application of one of these principles may be patented. *See, e.g., Bilski*, 130 S. Ct. at 3230 ("[W]hile an abstract idea, law of nature, or mathematical formula could not be patented, 'an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection.'" (quoting *Diehr*, 450 U.S. at 187)); *Funk Bros. Seed Co. v. Kalo Inoculant Co*, 333 U.S. 127, 130 (1948)

("If there is to be invention from such a discovery, it must come from the *application* of a law of nature to a new and useful end.") (emphasis added).

Prometheus's patent claims are directed to practical applications of metabolic processes to achieve a useful result, namely determining the optimum treatment range for a particular individual based on his or her personal metabolic rate. Such a diagnostic process can minimize the hazardous side effects of available medicines while at the same time optimizing their healing effect on a personalized basis. Furthermore, applying the "important and useful clue" of the machine-or-transformation test to determine patent eligibility, *Bilski*, 130 S. Ct. at 3226, Prometheus's process claims pass the physical transformation threshold for patent eligibility. As the Federal Circuit concluded, the "transformation is of the human body and of its components following the administration of a specific class of drugs and the various chemical and physical changes of the drugs' metabolites that enable their concentrations to be determined." *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1355-56 (Fed. Cir. 2010).

B. Any "Correlation" Recited in Prometheus's Claims Is Not a Law of Nature or a Physical Phenomenon.

Mayo repeatedly refers to that portion of Prometheus's claims directed to a "need to increase" or a "need to decrease" the amount of a drug later

administered to the patient as a "natural correlation between metabolite levels and patient health." *See, e.g.*, Mayo Br. at 6; *see also id.* at 5, 7, 13. Indeed, the theme of Mayo's brief is that Prometheus's invention is ineligible for patent protection because it claims a "natural correlation." *Id.* at 18. Mayo's own brief demonstrates that this is a misguided characterization. Specifically, Mayo makes much of the fact that it purportedly improved upon Prometheus's blood test. *Id.* at 8-10. Indeed, Mayo goes so far as to argue that Prometheus's patent claims reflect "disputable numbers." *Id.* at 40. If Prometheus's numbers can be so readily "improved upon" and "disputed," one must ask how they could possibly reflect a law of nature. They cannot.

Even assuming, however, that the numbers recited in the claim (i.e., "less that 230 pmol per $8x10^8$ red blood cells" and "greater than about 400 pmol per $8x10^8$ red blood cells") were "correct" and somehow "accurately" indicated any particular patient's need for an increase or decrease in the amount of drug delivered, such "correlation" is still not a law of nature or physical phenomenon of the type that is ineligible for patent protection under this Court's precedent. Simply put, this Court has never stated that a "correlation," as distinct from a law of nature or physical phenomenon, is ineligible for patent protection. *But see LabCorp*, 548 U.S. at 137 (Breyer, J., dissenting from dismissal of petition for writ of certiorari) (equating a "simple natural correlation" with a "natural phenomenon").

As a policy matter, "correlations," even those related to nature or the diagnosis of a disease, should be treated differently than physical phenomena or laws of nature. In explaining that laws of nature are excluded from patent protection, this Court in *Diehr* used as examples Einstein's fundamental law that $E = mc^2$ and Newton's law of gravity, observing that "[s]uch discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Diehr*, 450 U.S. at 185 (quoting *Chakrabarty*, 447 U.S. at 309). These examples demonstrate that the "law of nature" category that this Court has excluded from patent protection is directed at the most fundamental of physical principles. When such laws of nature are harnessed by human ingenuity into correlations that can be applied in practical and useful methods, such as methods of diagnosing or treating disease, patent protection should be available, and neither this Court nor Congress has ever said otherwise.

Indeed all of science is predicated on the observation of physical phenomena in order to discover "correlations" that are presumed to be consequences of the "laws of nature," even if the connection is not immediately apparent. Here, the inventors determined that metabolite levels below a certain amount (one variable) indicated a need to increase drug dosing (the other variable), and that metabolite levels above a certain amount (one variable) indicated a need to decrease dosing (the other variable). Those correlations are subject to interpretation and revision, as evidenced by Mayo's

arguments. Laws of nature and physical phenomenon, on the other hand, are not subject to the interpretation of the observer; they are truisms. They explain all observations of the known universe, e.g., the law of gravity or the theory of relativity.

Consider a pot of boiling water. When a pot of pure water is heated under 1 atmosphere of pressure, the water will always boil (i.e. convert from a liquid to a gas) at 100°C, because the underlying physical chemistry of water molecules causes this result. That is, it would be inconsistent with the laws of nature for the pot of water to boil at any other temperature because such effect reflects a law of nature and/or a physical phenomenon. Correlation based on that natural phenomenon, on the other hand, might relate to the observation of two variables associated with the pot of boiling water. For example, if the pot of boiling water were infused with certain botanicals (one variable), one might notice that campers near the pot of boiling water tended to receive fewer mosquito bites (the other variable). One could recite this correlation in a patent claim directed to a method of reducing the number of mosquito bites one receives while camping. Certainly such method, which applies a correlation to practical and useful effect, should be eligible for patent protection, if novel and non-obvious under other provisions of the patent statute.

The PTO has long recognized the patentability of diagnostic claims, including those that apply a biological correlation. Indeed, *Petitioners' own*

patent portfolio includes many patents directed to biological correlations. *See, e.g.*, Mayo's U.S. Patent 5,928,883, col. 9, ll. 12-20 (claiming "A diagnostic method comprising: obtaining a physiological sample of material from the gastrointestinal tract of a human [with] an inflammatory bowel disorder; and determining the level of the eosinophil pro-inflammatory granule protein eosinophil peroxidase in said sample, wherein the level is *correlated* to the presence or absence of said inflammatory bowel disorder.") (emphasis added); Mayo's U.S. Patent 6,235,486, col. 31, ll. 2-12 (claiming "A method for detecting or determining breast cancer in a human, comprising: a) contacting an amount of an antibody . . . with the cells of a human tissue sample so as to form a binary complex comprising the antibody and the cells; and b) determining or detecting the presence or amount of complex formation in the sample and *correlating* the presence or amount of said complex to the presence or absence of breast cancer in said human.") (emphasis added); and Mayo's U.S. Patent 6,475,723, col. 18, ll. 26-37 (claiming "A method for determining a diagnosis, prognosis or risk of a Tau pathology in a patient, said method comprising detecting a tau gene mutation in genomic DNA of the patient, wherein [the mutation has specified characteristics], and wherein said mutation is associated [i.e., correlates] with said Tau pathology.")

Thus, adopting Petitioners' view that "correlations" are the same as "natural laws" and/or "physical phenomena," would substantially "disrupt

the settled expectations of the inventing community." *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997)). As the Supreme Court warned in *Festo*, "[t]o change so substantially the rules of the game now could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired and which would be affected by [the] decision." 535 U.S. at 739 (quoting *Warner-Jenkinson*, 520 U.S. at 32 n.6).

Moreover, narrowing the interpretation of section 101 to exclude claims that include a biological correlation, like those in Prometheus's patents or for that matter in Mayo's patents, would have an unintended and chilling effect on the medical research industry. Medical research and diagnostic companies spend billions of dollars annually to develop new methods for diagnosing or predicting a susceptibility to disease, as well as new methods of making and testing drugs in order to ensure their safety and efficacy. Diagnostic tests to identify increased risk, to allow early detection, and to ensure safe and/or effective administration of drugs are vital to improving the health and quality of life throughout the world. Patent protection for diagnostic and therapeutic processes is necessary to ensure that the companies investing in medical research are adequately compensated for large development and regulatory costs. Patent protection provides a necessary incentive for others to invest in

similar research and development, leading to increased economic health as well as advancing the general well being of the public.

III. Petitioners' Many Complaints Are Appropriately Addressed by Other Provisions of the Patent Statute.

Understandably, one might be sympathetic at first to some of Petitioners' many complaints in this case. Mayo might be correct that Prometheus should not be allowed to assert its patents against Dr. el-Azhary's dermatological research. *See* Mayo Br. at 25. Mayo might be correct that claims in the Prometheus patent are "vague and open-ended." *See id.* at 44. Mayo might be correct that "the method of blood testing for metabolites are well known and have been used by physicians and researchers for decades." *See id.* at 24. These issues, however, are not presently before this Court. More importantly, they are not appropriately addressed under section 101 of the patent statute—the patent statute has other provisions that squarely address these concerns with requirements that the claimed invention is new, nonobvious and clearly disclosed.[5]

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[5] See 35 U.S.C. §§102, 103, 112. AIPLA takes no position on whether these defenses apply to the Prometheus claims in this case or that Mayo would prevail on any one of them. AIPLA intends simply to explain how the comprehensive patent statute has other provisions that more appropriately and more directly address the complaints Mayo has raised before this Court.

See also Brief for the United States As Amicus Curiae Supporting Neither Party at 26-32.

For example, Petitioners' complaint that Prometheus is inappropriately asserting its claims in the field of dermatological research should be addressed as an issue of claim construction. Notably, the claim at issue recites a method "for treatment of an immune-mediated gastrointestinal disorder." U.S. Patent 6,355,623, col. 20, ll. 9-10. The claim further requires administering a drug to a subject "having said immune-mediated gastrointestinal disorder." *Id.* at col. 20, ll. 13-14. Certainly such claim language might appropriately be construed as a matter of law by a court as excluding methods for the treatment of dermatological disorders. *See Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 391 (1996).

Similarly, Petitioners complain that Prometheus asserts that its patents cover treatment for "all types of autoimmune diseases." Mayo Br. at 24. Petitioners might rely on Section 112, paragraph 1, in defense of such argument. Section 112, paragraph 1, requires the patentee to provide "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art . . . to make and use the same." 35 U.S.C. § 112, ¶ 1 (2006). This statutory provision provides two separate requirements for patentability: (1) the written description requirement, and (2) the enablement requirement.

See Ariad Pharm., Inc. v. Eli Lilly and Co., 598 F.3d 1336, 1344 (Fed. Cir. 2010) (en banc). As explained by the Federal Circuit, "[t]he purpose of the written description requirement is to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.'" *Id.* at 1353-54 (citation omitted). Here, it could be argued that Prometheus has not described any invention beyond the treatment of immune-mediated gastrointestinal disorders. Therefore, the patent might be invalid for failing to satisfy the written description requirement, if the claims are construed any more broadly than that. *See id.* at 1358 (holding patent claims invalid for lack of written description).

Similarly, Mayo's complaint that Prometheus's claims are vague and open-ended might be appropriately be addressed under the second paragraph of section 112 of the patent statute, which requires that a patent "conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2 (2006). This statutory provision has been applied to hold vague and open-ended claims invalid as indefinite. *See Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1356 (Fed. Cir. 2005) (invalidating patent claims for indefiniteness under 35 U.S.C. § 112, ¶ 2).

Finally, Mayo's contention that the claimed process is well known and has been used for decades might appropriately be addressed under sections 102 and 103 of the patent statute. Section 102 sets forth the requirement for novelty of the claimed invention. 35 U.S.C. § 102 (2006); *see, e.g., Brown v. 3M*, 265 F.3d 1349, 1353 (Fed. Cir. 2001) (invalidating patent claims under 35 U.S.C. § 102 for lack of novelty). Section 103 sets for the requirement of non-obviousness of the claimed invention. 35 U.S.C. § 103 (2006); *see, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 13 (1966) (invalidating patent claims under 35 U.S.C. § 103 as obvious in view of the prior art). Thus, if Prometheus's claims are directed to well known methods or even obvious variations of well known methods as Petitioners allege, the claims might be invalid under sections 102 or 103 of the patent statute.

Petitioners urge that the cases upon which they rely do "not improperly import novelty and obviousness analysis into Section 101 from Sections 102 and 103" because "[s]ection 101 on its face limits patentable subject matter to a 'new and useful process.'" Mayo Br. at 36 (quoting *Parker v. Flook*, 437 U.S. 584, 591, 594 (1978)). But this Court has squarely rejected that argument:

> It has been urged that novelty is an appropriate consideration under § 101. Presumably, this argument results from the language in § 101 referring to any "new and useful" process, machine, etc. Section 101,

> however, is a general statement of the type of subject matter that is eligible for patent protection "subject to the conditions and requirements of this title." Specific conditions for patentability follow and § 102 covers in detail the conditions relating to novelty. *The question therefore of whether a particular invention is novel is "wholly apart from whether the invention falls into a category of statutory subject matter."*

Diehr, 450 U.S. at 189-90 (emphasis added) (footnote omitted) (quoting *In re Bergy*, 596 F.2d 952, 961 (C.C.P.A. 1979). Thus, rather than rely on section 101 of the patent statute to defend this case, Petitioners should rely on the many other provisions of the patent statute available to them.

IV. Patent Protection is Vital to the Personalized Medicine Industry.

The impact of patent protection varies from industry to industry, but it is particularly critical to medical research industries such as pharmaceuticals, biotechnology, and personalized medicine. Medical research companies spend billions of dollars annually to develop new methods for diagnosing or predicting susceptibility to disease as well as new methods of making and testing drugs in order to ensure their safety and efficacy. Dep't of Health & Human Services, *Personalized Health Care: Pioneers, Partnerships, Progress* at 79 (2008). Diagnostic tests to identify increased risk of disease, to allow early detection of disease, and to ensure safe

and/or effective administration of drugs are vital to improving the health and quality of living throughout the world. Patent protection for diagnostic processes is necessary to ensure that the companies investing in medical research are adequately compensated for large development and regulatory costs and to provide incentives for others to invest in similar research and development. Committee on Intellectual Property Rights in Genomic and Protein Research; National Research Council, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health* at 20 (Merrill & Mazza eds., 2006). Thus, patent protection leads to increased economic health as well as advancing the general well being of the public.

Personalized medicine, in particular, is a nascent but growing industry focused on the development of therapies specific to the needs of individual patients. Personalized medicine designs therapies around a given patient's unique physiology, such as a particular patient's ability to metabolize a particular drug. R. Mullin, *Personalized Medicine*, 86 Chemical & Engineering News at 17-27 (Feb. 11, 2008); M. Aspinall and R. Hammermesh, *Realizing the Promise of Personalized Medicine*, 85 Harv. Bus. Rev. 109 (Oct. 2007). This approach to treatment avoids the high costs (in terms of lives and dollars) of the traditional trial and error approach to diagnosis and treatment. A notable example of personalized medicine is the development of a diagnostic test for sensitivity to the

blood-thinning drug Warfarin. Prior to the development of that new test, the traditional trial and error approach resulted in under- and overdosing that was estimated to cost the healthcare system over a billion dollars annually due to serious bleeding and strokes. HHS *Personalized Health Care* at 13; A. McWilliam, et al., *Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin,* AEI-Brookings Joint Center for Regulatory Studies at 2-3 (Nov. 2006). Another example of personalized medicine is the identification of biomarkers of certain cancers. Once identified, these biomarkers may be used to determine whether a patient's particular cancer is effectively treated by a certain drug that may have significant side effects. *See* PricewaterhouseCoopers LLP, *The New Science of Personalized Medicine: Translating the Promise into Practice* at 7 (Oct. 2009) (describing a companion diagnostic test for determining whether administering Herceptin® (trastuzumab) to treat breast cancer will be effective).

One of the greatest challenges facing the personalized medicine industry is obtaining funding for the necessary clinical research. *See* HHS, *Personalized Health Care* at 83. The availability of patent protection is essential to obtaining that funding. A ruling that novel and nonobvious diagnostic methods are ineligible for patent protection would cripple the nascent personalized medicine industry, to the detriment of the public.

CONCLUSION

For the foregoing reasons, AIPLA urges the Court to find Prometheus's patent claims eligible for patent protection under section 101 of the patent statute.

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AMICUS CURIAE BRIEF

RECORD
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BRIEFS

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In the Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES)
AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

On Writ of Certiorari
to the United States Court of Appeals
for the Federal Circuit

BRIEF FOR ARUP LABORATORIES, INC. AND LABORATORY CORPORATION OF AMERICA HOLDINGS (D/B/A LABCORP) AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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INTERESTS OF *AMICI CURIAE*[1]

Amici are leading clinical laboratory companies. Like Petitioners, *amici* are in the business of analyzing blood specimens to aid in diagnosis, treatment, and prevention of disease. And like Petitioners, *amici* have active research programs through which they develop cutting-edge and life-saving assays and diagnostic techniques.

Amicus ARUP Laboratories, Inc. ("ARUP") is a nationally renowned medical reference laboratory. ARUP is an enterprise of the University of Utah and its Department of Pathology. Offering highly complex and unique lab tests, ARUP provides screening services, as well as molecular and genetic assays with accompanying consultative support. ARUP's tests cover numerous medical fields including allergy and immunology, chemistry, cytogenetics, endocrinology, fetal risk assessment, genetics, hematology, hepatitis and HIV, infectious diseases, neurology, oncology, and pathology. ARUP processes nearly 35,000 tissue and fluid specimens every day. Medical directors and genetic counselors are on staff at ARUP and provide consultation and result interpretation. ARUP's clients include more than half of the

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[1] All parties to this case have consented to the filing of this brief, and their consents have been filed with the Clerk of this Court. No counsel for any party had any role in authoring this brief, and no person other than the named *amici* and their counsel has made any monetary contribution to the preparation and submission of this brief.

nation's university teaching hospitals and children's hospitals, as well as regional hospital networks, multihospital groups, major commercial laboratories, group purchasing organizations, military and government facilities, and major clinics.

Amicus Laboratory Corporation of America Holdings ("LabCorp") is the country's second largest independent clinical laboratory company whose 31,000 employees perform more than 270 million tests annually for more than 220,000 clients. LabCorp is a pioneer in commercializing new diagnostic technologies and the first in the industry to embrace genomic testing. Additionally, LabCorp was the petitioner in *Laboratory Corporation of America Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) ("*LabCorp*") (dismissing writ of certiorari as improvidently granted), which concerned a patented method of detecting certain vitamin deficiencies. The method consisted of just two steps: (1) measure the levels of a particular amino acid in the body, and (2) recognize that elevated levels of the amino acid are correlated with certain vitamin deficiencies. LabCorp was accused of inducing infringement every time a doctor ordered its amino acid assay. The issue presented in this current case before the Court is strikingly similar to that of the *LabCorp* case and provides this Court the opportunity to confirm that natural phenomena and laws of nature cannot be removed from the public domain through creative use of the patent laws as Respondent seeks to do here.

Amici have a compelling interest in this case. Just as in *LabCorp*, the Federal Circuit has once again allowed a patent-holder to claim ownership of

a basic scientific phenomenon: the correlation between levels of a particular drug in the blood and patient health. *Amici*'s research activities, as well as the diagnostic services they offer to hospitals, physicians, and managed-care organizations across the country, depend on this type of scientific knowledge. *Amici* agree with Petitioners' arguments and submit this brief to explain further that the Federal Circuit's decision allows patentees and litigants to inhibit advancements in medical science and clinical services by asserting a monopoly over basic scientific phenomena.

INTRODUCTION AND SUMMARY

The question presented in this case concerns the scope of patentable subject matter under the Patent Act of 1952. The Act provides: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. Although the scope of patentable subject matter is thus broad, it is settled precedent that it does not extend to natural phenomena. "The Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'" *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)); *see also Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

The correlation described in the patents at issue in this case is a scientific fact — a law of nature — relating drug levels to health in the human body. The patents assert exclusive rights over the process

of administering a drug and observing the results. This is improper. Whatever biochemical reaction occurs in a patient's body is not the subject of the patent laws, but rather is a natural phenomenon. These patents are not directed to new and unique medicines, reagents or testing equipment. They are directed instead to the basic concept of measuring drug levels and deciding a patient's relative health. This not only blocks the mental work of doctors advising patients, but also impedes the progress of research by seeking to own a basic law of nature concerning the human body's reaction to drugs. The preemptive effects of such patents on research, medical services and the growing field of personalized medicine are profound.

In crossing over the line between patents on human invention and patents on nature itself, the patent claims in this case upset the "careful balance" struck by the patent laws that is "the very lifeblood of a competitive economy." *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989). A United States patent confers upon its owner the powerful right to exclude others from practicing whatever invention is claimed in the patent for a defined period of time. *See* 35 U.S.C. § 271 (defining infringement); *id.* § 154 (20-year term). Such a right to exclude can also extend to the substantial equivalent of the patented invention. *See, e.g., Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 21 (1997). Such powerful rights should not be conferred upon claims on laws of nature.

The Prometheus patents and others like them allow no room to design around, imitate, or improve upon the so-called "invention" of a law of nature.

Doctors and laboratories test patients' blood and routinely evaluate the laws of nature in providing health care. But if claims like the ones at issue are sustained, such tests may be blocked by patents on the law of nature on which they are based. This is especially harmful given the nature of modern medicine, which allows doctors and reference laboratories to efficiently measure a battery of markers and conditions to diagnose and treat patients.

By contrast, invalidating the claims and reaffirming the principle set forth in *Diehr* and confirmed in *Bilski* will not disrupt or impede scientific research. Inventors and companies can and will file for patents for novel medicines, reagents, equipment and the like, including processes for using these inventions. Patent lawyers, however, should not be permitted a "land grab" to block use of underlying laws of nature. Reversing the Federal Circuit will simply restore the balance between natural phenomena and human-made inventions that Congress originally sought to strike in the patent laws — a balance that reflects the Constitution and has served the patent system and the progress of science very well. The decision below should be reversed.

ARGUMENT

I. THE PATENTS IMPROPERLY REMOVE A NATURAL PHENOMENON FROM THE PUBLIC DOMAIN

A. Patentable Subject Matter Does Not Include Laws Of Nature, Natural Phenomena, Or Abstract Ideas

Congress intended the scope of patentable subject matter to be broad and inclusive, even for tech-

nologies that had yet to be imagined. The Committee Reports accompanying the 1952 Patent Act provide that Congress intended statutory subject matter to "include anything under the sun that is made by man." S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952), quoted in *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

But Congress likewise established just and appropriate limits to the reach of the patent statutes. The patent laws protect only *inventive* products and processes. Thus not every discovery is necessarily patentable. A bedrock principle of United States patent law is that: "Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981) (citations omitted). Accordingly:

> [A] new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none."

Chakrabarty, 447 U.S. at 309 (*quoting Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)); *see also Parker v. Flook*, 437 U.S. 584, 593 n.15 (1978) ("[R]ecognition of a theretofore existing phenomenon or relationship carries with it no rights to exclude others from its enjoyment." (quoting P. Rosenberg, *Patent Law Fundamentals*, § 4, p. 13 (1975)); *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) ("Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are

not patentable, as they are the basic tools of scientific and technological work.").

"[T]hese exceptions have defined the reach of the statute as a matter of statutory *stare decisis* going back 150 years." *Bilski*, 130 S. Ct. at 3225 (citing *Le Roy v. Tatham*, 55 (14 How.) 156, 174-75 (1853)). This Court thus has properly hesitated to alter the fundamental concepts of patent law that have guided generations of inventors and succeeded in furthering the progress of science and useful arts. *See Bd. of Trs. of Stanford Univ. v. Roche Molecular Sys., Inc.*, 131 S. Ct. 2188, 2198-99 (2011).

As pointed out by Justice Breyer in *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006) ("*LabCorp*"), a case presenting a question similar to that presented here, the justification for this longstanding principle is that too much patent protection can impede scientific progress, and that fundamental scientific principles are "part of the storehouse of knowledge" available to all. *Id.* at 127 (Breyer, J., dissenting from dismissal of writ as improvidently granted) (quoting *Funk Bros.*, 333 U.S. at 130).

Whether a claimed invention is a valid subject matter for a patent under these principles has been the subject of various decisions of this Court since the 1952 Patent Act became law. In several of these decisions, the Court upheld the patentability of the subject matter. In *Chakrabarty*, for example, the Court held that human-made bacteria exhibiting characteristics different from any bacteria occurring in nature are patentable subject matter. 447 U.S. at 310. In *Diehr*, the Court held that a computerized industrial process for control of a rubber curing mold

is patentable, even though the process "admittedly employs a well-known mathematical equation." 450 U.S. at 187. And in *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124 (2001), the Court held that newly developed plant breeds are patentable subject matter. *Id.* at 145.

In several other decisions, however, the Court held the subject matter of a patent to constitute a law of nature beyond the scope of the Act. In *Parker v. Flook*, for example, the Court held that a process for monitoring chemical reactions by using a mathematical formula is not patentable. *See* 437 U.S. at 594. And in *Gottschalk v. Benson*, the Court held that a process related to converting decimals to binary numerals using a formula is not patentable. *See* 409 U.S. at 71-72.

The distinction between the two lines of cases turns on whether the patent holder seeks to preempt the underlying law of nature, precluding others from testing or observing it. As the Court noted in *Diehr*, "an *application* of a law of nature . . . to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187 (emphasis in original). The Court found such an application in *Diehr* because, in that case, the patent holders "do not seek to pre-empt the use of that equation" but "seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process." *Id.* In contrast, the Court in *Gottschalk* found no patentable subject matter where "the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself." 409 U.S. at 72.

The distinction between the two lines of cases also turns, in the case of method claims like the ones at issue in this case, on whether the patented process is transformative. In analyzing the patentability of a claimed process, both *Diehr* (which upheld a claimed process) and *Gottschalk* (which struck down a claimed process) focused on the *end result* of the process. *See Diehr*, 450 U.S. at 184. Although transformation "is a useful and important clue, an investigative tool" for determining whether a patent on a claimed process is valid, it is not the sole test. *Bilski*, 130 S. Ct. at 3227.

For the reasons that follow, the Prometheus patent claims are on the non-patentable side of this well-established line because they involve no such transformation and seek to preempt all use by others of a basic natural phenomenon.

B. The Prometheus Claims Improperly Assert Exclusive Rights To Measure And Observe A Natural Phenomenon — Namely, That Certain Levels Of 6-Thioguanine Correlate To Patient Health

The Prometheus claims are directed to a natural phenomenon. As exemplified by claim 1 of U.S. Patent No. 6,355,623, the "process" for which Prometheus asserts exclusive rights is simply two steps: *administering* a drug and *measuring* the drug level in the patient:

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Once the measurement is done, the results can assist a doctor in determining a course of treatment. The patent fully admits that the drugs for treatment of gastrointestinal diseases were known in the art. The "discovery" that the patent owner seeks to keep for itself is the correlation between drug levels and medical decisions. This correlation, however, should not be patentable.

It is critical to note that the patient's health remains the same whether or not the measurement is done. The drug will have its effect with or without the measurement. It is also critical to note that Prometheus did not invent the drug in question. Nor did Prometheus invent any novel testing equipment or process. Any method of testing meets the claim. Any test infringes. Thus, testing labs such as ARUP and LabCorp could be accused of infringement by

providing results to doctors, and doctors would be accused of infringement by advising their patients and obtaining measurements of their patient's blood specimens. As Justice Breyer observed with respect to similar patents on a law of nature, "[a]t most, respondents have simply described the natural law at issue in the abstract patent language of a 'process.' But they cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge." *LabCorp*, 548 U.S. at 137.

The Prometheus claims are not applications of a scientific principle that might properly enjoy patent protection, such as the industrial process for molding rubber products in *Diehr*. *See Bilski*, 130 S. Ct. at 3230. Instead, these claims simply take a medical concept (administer a drug and measure for the drug in a patient) and apply it to a natural phenomenon occurring in the human body. This is not an industrial process that transforms one chemical into another; it is the discovery of a correlation between a particular drug and health state, and allowing such a discovery to be patented would improperly remove that natural correlation from the "storehouse of knowledge."

II. ALLOWING THE PROMETHEUS CLAIMS WOULD UPSET THE PATENT BALANCE CAREFULLY STRUCK BY CONGRESS AND THIS COURT AND WOULD HARM LIFE SCIENCES RESEARCH AND PATIENT CARE

The Constitution requires that patents "promote the Progress of Science and useful Arts." Art. I, § 8, cl. 8. Fulfilling this constitutional purpose re-

quires a balance between rewarding existing research and ensuring that other research may go forward freely in the future. Allowing a patentee to remove a natural phenomenon from the public sphere would thwart this constitutional purpose by impeding rather than promoting the progress of biochemical research and medical treatments. Without access to testing and observing natural phenomena, medical researchers cannot build upon the discoveries of others and doctors cannot treat their patients.

Allowing claims such as the ones at issue here would block medical information based on natural, biochemical relationships from appropriate further scientific use. This impediment would be especially acute with respect to the information being tested in patients' blood. Disallowing claims such as those being asserted by Prometheus, by contrast, will cause little harm to scientific progress because a wide range of other appropriate claims would remain available to researchers like Respondent. Therefore, the balance struck in *Diehr* and related cases on the scope of patentable subject matter should be preserved.

A. Existing Limitations On The Scope Of Patentable Subject Matter Reflect A Careful Balance Between Rewarding Existing Research And Ensuring Opportunity For Future Innovation

Patents fundamentally balance free competition against government-granted exclusive rights. "The Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any

concomitant advance in the 'Progress of Science and useful Arts.'" *Eldred v. Ashcroft*, 537 U.S. 186, 215 (2003) (quoting *Bonito Boats*, 489 U.S. at 146); *see also Mazer v. Stein*, 347 U.S. 201, 219 (1954) (noting that the patent system is based upon the "conviction that encouragement of individual effort by personal gain is the best way to advance public welfare through the talents of authors and inventors").

Patent law persistently seeks to strike a balance between these competing interests. Some features of patent law ensure adequate returns to the large fixed costs of research and development. For example, Congress has decided upon a 20-year term for patents. *See* 35 U.S.C. § 154. And by denying an independent creation defense to patent infringement, this Court has permitted liability to attach even if a person has no knowledge of the patent. *See Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 477 (1974). Other features of patent law seek to preserve opportunities for future innovation. For example, there is a statutory safe harbor for activities that would otherwise constitute patent infringement, so long as they are undertaken for purposes reasonably related to the development and submission of information under a federal law that regulates drugs. *See* 35 U.S.C. § 271(e); *see also Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990) (exemption applies to medical devices); *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 203-05 (2005) (exemption applies to preclinical research).

The definition of what constitutes patentable subject matter likewise reflects a balance that has been struck by Congress in section 101 of the Patent Act and by this Court in interpreting that section.

This balance — which distinguishes between natural phenomena and human-made inventions — has served the United States patent system and the progress of science in the nation very well.

The key to this balance is the recognition that there are interests in promoting innovation on both sides of any patent. As this Court stated in a different context in *Bonito Boats*, "[f]rom their inception, the federal patent laws have embodied a careful balance between the need to promote innovation and the recognition that imitation and refinement through imitation are both necessary to invention itself and the very lifeblood of a competitive economy." 489 U.S. at 146. As Justice Breyer has noted in the related context of copyright law, in ensuring a balance between preserving incentives to intellectual property holders and protecting the rights of others to develop new technologies, it is important to be sure that "the gains on the copyright swings would exceed the losses on the technology roundabouts." *Metro-Goldwyn-Mayer Studios, Inc. v. Grokster, Ltd.*, 545 U.S. 913, 960 (2005) (Breyer, J., concurring).

Here, allowing claims like those of Prometheus would cause serious "losses on the technology roundabouts," upsetting the balance that Congress and this Court have long struck with respect to patenting laws of nature. By precluding scientific inquiry (i.e., the ability to test, observe, and conclude) into naturally occurring phenomena, enforcing Prometheus' patents and others like it would remove the common tools accessible to all scientists that allow scientific progress to be made. Invalidating Prometheus' patents, by contrast, would still allow wide berth for patenting truly transformative human in-

ventions that add to rather than subtract from the public domain.

B. Allowing The Prometheus Patents To Stand Would Impede Future Biomedical Research And Treatment That Depends Upon Common Access To Natural Phenomena

Science has always proceeded in an incremental way in which one discovery builds upon another. Experts in the scientific method have accordingly noted that scientific progress requires that research results be open for all to "use, attempt to replicate, and evaluate." U.S. Nat'l Research Council Committee on Intellectual Property Rights in the Knowledge-Based Economy, *A Patent System for the 21st Century* 26 (2004). This aspect of scientific progress would be impeded if patents could extend to natural phenomena. The Council of the [United Kingdom] Royal Society has drawn a parallel implication:

> [P]ure knowledge about the physical world should not be patentable under any circumstances. That it should be freely available to all is one of the fundamental principles of the culture of science. Only by having knowledge unencumbered by property rights can the scientific community disseminate information and take science forward.

Royal Society Working Group on Intellectual Property, *Keeping Science Open: The Effects of Intellectual Property Policing on the Conduct of Science* 8 (April 2003).

Whatever the effect of the scope of patentability on scientific research in the past, however, these principles are even more important to the next generation of biomedical research. The nature of the information contained within the genetic code presents new and unique incentives to try to own natural phenomena. Any holding that one may effectively own a natural biochemical relationship by excluding others from any and all testing of that relationship thus would have especially fundamental implications for future research in the field of DNA and human genetic conditions.

Likewise, valuable blood-testing and treatment of patients would be discouraged by allowing patent claims covering the most basic of medical practices — administering medicine and observing the results — to be applied to newly discovered natural phenomena.

ARUP itself publishes natural phenomena that its scientists discover in the course of their research and clinical testing.[2] These publications provide to the public domain information about hereditary diseases and genetics — information that

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[2] *See, e.g.*, C.P. Vaughn, J. Robles, J.J. Swensen, C.E. Miller, E. Lyon, R. Mao, P. Bayrak-Toydemir, W.S. Samowitz, *Clinical Analysis of PMS2: Mutation Detection and Avoidance of Pseudogenes*, 31 HUMAN MUTATION 588-93 (2010); F. Gedge, J. McDonald, A. Phansalkar, L.S. Chou, F. Calderon, R. Mao, E. Lyon, P. Bayrak-Toydemir, *Clinical and Analytical Sensitivities in Hereditary Hemorrhagic Telangiectasia Testing and a Report of* de Novo *Mutations*, 9 J. MOLECULAR DIAGNOSTICS 258-65 (2007); D.K. Crockett, G. Pont-Kingdon, F. Gedge, K. Sumner, R. Seamons, E. Lyon, *The Alport Syndrome* COL4A5 *Variant Database*, 31 HUMAN MUTATION E1652-57 (2010).

existed in nature but required the effort and creativity of ARUP scientists and others to find. These discoveries allow for inventions to be created and for doctors to treat patients more effectively. Similarly, the tests that laboratories like ARUP and LabCorp run on patient samples measure the amount of drugs or markers, or the presence of genetic conditions, in the body, all of which are natural phenomena. These results or conditions would exist in the patients whether or not the measurements took place.

In contrast, if patents like those asserted by Prometheus were allowed to stand, all such naturally occurring biochemical relationships would be subject to ownership rights on the part of the person who discovers them. For instance, if the effect of a drug in the body creates condition "X", the person who discovers this relationship might seek a patent covering all measurement of condition "X" or all evaluation of condition "X" by a doctor treating a patient. This is not a human-made invention, but a scientific discovery — and a patent to such a discovery would remove from the "storehouse of knowledge" that which should be free for all to use. Patents that claim the underlying natural phenomena and biochemical relationships will greatly impede medical research that builds upon the discovery of scientific facts.

For these reasons, there are special dangers in allowing only one laboratory or entity exclusive rights to the results of a natural phenomenon in the human body. Science will advance more rapidly, with benefits to patients, if laboratories may both compete with and collaborate with one another through common access to laws of nature.

C. Invalidating Prometheus' Patents Would Neither Eliminate Incentives To Invest In Research Nor Disrupt The Patent System

The state of the law with respect to ownership of biochemical relationships is relatively unsettled. This has resulted in a well-documented "land-grab" mentality, in which patent attorneys seek patents at the outer boundaries of the line between human invention and natural phenomena. This is not surprising, for without guidance about the scope of valid versus invalid subject matter, patent attorneys are obliged to seek the broadest possible claims for their clients. *See Solomon v. Kimberly-Clark Corp.*, 216 F.3d 1372, 1382 (Fed. Cir. 2000) (a patent attorney has a "professional responsibility . . . to assist his or her client in defining her invention to obtain, if possible, a valid patent with maximum coverage").

Just because these pressures have led patent attorneys to seek and sometimes obtain patents that stretch the boundaries of patentability into the natural realm, however, does not mean that such increased scope is necessary to advances in science. This case presents a vital opportunity for the Court to curb this pressure on the outer boundaries of patentability, and to return the balance to the baseline set in *Diehr* and related decisions. There is little danger that so doing will harm genetic or other biomedical research by reducing incentives for making discoveries.

This is so for two reasons. *First*, nothing in the argument advanced by *amici* here would impede patents in the genetic area if those patents involved more than the mere observation and recitation of a

law of nature. Consistent with this Court's test in *Diehr*, patent claims may be appropriate as directed to applications of laws of nature such as new drugs, reagents, or equipment. Thus the scope of patentable subject matter still may legitimately extend to innovative tests, or inventive pharmaceutical compositions, or new and useful therapies, or any number of inventions in technology that researchers have yet to imagine, that add human invention to a natural phenomenon. The issue here, by contrast, is whether ownership rights should be permitted to result from the mere discovery of the phenomenon.

Second, invalidating claims like those of the Prometheus patent will not necessarily invalidate any patents per se. Claims define the metes and bounds of what the patent holders consider their exclusive rights. Each claim defines the scope of a different invention. 35 U.S.C. § 112. Patents contain multiple claims because patent applicants are allowed to claim several inventions based upon a single technical disclosure. Indeed, standard patent practice is to file a number of claims of varying scope precisely to protect against future uncertainty. Broad claims have the greatest coverage, but the highest likelihood of being invalidated (for example, by prior art). Narrow claims have the best chance of avoiding prior art, but offer the least coverage. Thus, one does not infringe a patent; one infringes a patent claim. Likewise, a court does not determine that a patent is invalid; it determines whether some or all of the claims are invalid.

D. If There Is Any Ambiguity About The Patentability Of Natural Phenomena, It Should Be Resolved In Favor Of Petitioner In Order To Avoid Serious Constitutional Questions

Just as this Court interpreted copyright law so as to ensure consistency with the Constitution, *see Feist Publ'ns, Inc. v. Rural Tel. Serv. Co., Inc.*, 499 U.S. 340 (1991), so too should it interpret patent law. There are two constitutional problems with the patent claim at issue in this case, and with all patents claiming exclusive rights to the results of a measurement of nature.

First, patents on measurements of nature, like the copyright struck down in *Feist*, deal with facts themselves. The corresponding lack of originality raises serious questions under Article I, which gives Congress authority to issue patents that "promote the Progress of Science and useful Arts." U.S. Const. art. I, § 8, cl. 8. Patents on measurements of nature take information out of the public domain rather than putting ideas into the public domain provided for in the Constitution and of the patent disclosure provisions. *See* 35 U.S.C. § 112. In the present case, for example, a scientist or doctor was free before the patent issued to measure the level of 6-thioguanine in a blood sample and correlate that with the patient's health. It was infringement to do so, however, after the patent issued. The subject matter provision of the Patent Act, 35 U.S.C. § 101, therefore should be interpreted to prohibit patents that preempt the use of principles or measurements of nature and that, in effect, bar future researchers from making

such measurements or from using information that is available from nature. Patents that have such effects do not "promote the Progress of Science."

A second constitutional difficulty with patent claims on measurements of nature is that the patent may have a significant chilling effect on publication in violation of freedom of speech principles protected by the First Amendment. Under normal patent law principles, if the Prometheus claim is valid, a scientist, doctor, or medical firm publishing an article encouraging the use of a 6-thioguanine measurement as a way of optimizing drug therapy might be found to have induced infringement under 35 U.S.C. § 271(b) ("Whoever actively induces infringement of a patent shall be liable as an infringer.").

No scientist, doctor, or laboratory should need to undertake an analysis of the intent requirements for inducing infringement before publishing a research article on the interactions of a known medicine and the human body. A spread of such patents would have an enormous chilling effect on scientific and commercial publication.

These constitutional considerations should provide an additional reason to reaffirm the *Diehr* principle by ruling for Petitioners in this case.

CONCLUSION

The judgment of the court of appeals should be reversed.

Respectfully submitted,

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September 9, 2011

AMICUS CURIAE BRIEF

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (d/b/a MAYO MEDICAL LABORATORIES) and MAYO CLINIC ROCHESTER,

Petitioners,

—v.—

PROMETHEUS LABORATORIES, INC.,

Respondent.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICI CURIAE* ASSOCIATION INTERNATIONALE POUR LA PROTECTION DE LA PROPRIÉTÉ INTELLECTUELLE AND INTERNATIONAL ASSOCIATION FOR THE PROTECTION OF INTELLECTUAL PROPERTY (U.S.) IN SUPPORT OF NEITHER PARTY

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I. INTEREST OF AMICI CURIAE[1]

This brief is submitted on behalf of *amici curiae* Association Internationale Pour La Protection De La Propriété Intellectuelle ("AIPPI") and International Association For The Protection Of Intellectual Property (U.S.) ("AIPPI-US") (hereinafter referred to collectively as "AIPPI").

AIPPI is an international organization, founded in 1897, dedicated to the development, improvement, and legal protection of intellectual property. AIPPI is a politically neutral, non-profit organization headquartered in Switzerland having over 9000 members representing over 100 countries and operating mainly through National and Regional Groups, such as the AIPPI-US.

The members of AIPPI include intellectual property lawyers, patent and trademark attorneys, and patent agents in corporate and private practice throughout the world, as well as academics and other persons interested in intellectual property, and including members from North America, South America, Europe, Asia, Australia, and Africa.

The primary goals of AIPPI, in accord with its implementing statutes and regulations, are to promote the protection of intellectual property on a national and international basis and to study and

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[1] The parties have consented to the filing of this brief. No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than the Amici has made a monetary contribution to the preparation or submission of this brief.

compare existing law and proposed laws to propose improvements thereto. AIPPI pursues these objectives, in part, by working for the development, expansion and improvement of international and regional treaties and agreements and also of national laws relating to intellectual property. In its long history, AIPPI has adopted more than 700 Resolutions and Reports. An AIPPI "Resolution" is a Statement of Policy regarding a specific Intellectual Property issue, approved by the collective National and Regional Group members of AIPPI. Such a Resolution is issued only after lengthy study and discussion and subsequent vote by a majority of delegates present at an Annual Meeting of the Executive Committee of AIPPI. The presentation of these Resolutions and Reports to international Governmental Organizations, in particular the World Intellectual Property Organization ("WIPO"), has contributed considerably to the development, improvement and harmonization of the international protection of intellectual property. AIPPI has adopted a Resolution on an issue touching that before this Court: Resolution Q202 ("The impact of public health issues on exclusive patent rights"), discussed below and attached hereto (Appendix at A1-A5).

For at least the above-noted reasons, and on behalf of both resident and non-resident AIPPI members who seek, on behalf of the clients they represent, clarity in the applicability of patent rights in the United States to methods of medical treatment of patients, AIPPI submits this brief to this Court.

II. INTRODUCTION

The framers of the United States Constitution recognized the need to encourage innovation, and dissemination of the same, by rewarding inventors and granted the United States Congress the authority "[t]o promote the Progress of . . . useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their . . . Discoveries." U.S. Const. art. I, § 8, cl. 8. Congress enacted the first United States Patent Act in 1790 requiring, *inter alia*, the applicant to "have invented or discovered any useful art, manufacture, engine, machine, or device, or any improvement therein." Patent Act of 1790, ch. 7, § 1, 1 Stat. 109 (April 10, 1790). Congress amended this Act in 1793 to require that the applicant "have invented any new and useful art, machine, manufacture or composition of matter, or any new and useful improvement." Patent Act of 1793, ch. 11, § 1, 1 Stat. 318 (February 21, 1793). In the revisions to the Patent Act of 1952, Congress amended the language of 35 U.S.C. § 101 to use the term "process" in lieu of "art," stating: "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." The Patent Act of 1952 further required the subject matter of the invention to be novel (*see* 35 U.S.C. § 102), to be non-obvious (*see* 35 U.S.C. § 103), and to satisfy certain disclosure requirements (*see* 35 U.S.C. § 112).

The United States has been historically, and remains currently, a leader in innovation. Manufacturing, chemistry, electronics, biotechnology,

and computer software are just a few of the technological fields that have seen tremendous commercial development within the United States. The Patent Laws of the United States have accommodated and fostered innovation in and development of all of these technologies, and have helped the United States to achieve and maintain its position in the global economy.

Nearly all developed and developing nations worldwide have patent laws that likewise seek to foster innovation in and development of important technologies and advancements for their own societies and for the global society at large. In one important respect, however, the patent laws of the United States differ from those of virtually all other nations (the sole exception being Australia): only in the United States (and Australia) are methods of medical treatment of patients considered patent-eligible subject matter. Because this important distinction sets U.S. patent law apart from the patent laws of nearly every other country around the globe, the applicability of exclusive patent rights to methods of medical treatment of patients raises unique concerns for all people who seek medical treatment in the United States.

In 1996, Congress addressed these concerns at least partially by enacting 35 U.S.C. § 287(c), which eliminates a patentee's remedy by civil action, and the right to injunction, damages, and attorney fees against medical practitioners and related health care entities for the performance of certain patented medical procedures.

This brief attempts to serve the Court by providing both a global perspective on the issue of patent eligibility for methods of medical treatment

of patients, and a commentary on the effectiveness and impact of the current U.S. statutory scheme affecting this issue. Finally, AIPPI urges that federal subject matter jurisdiction is lacking here, in light of that U.S. statutory scheme.

III. SUMMARY OF THE ARGUMENT

AIPPI's mandate is to study the way patent systems around the world protect intellectual property and make recommendations for improvement. To this end, AIPPI has studied the particular limitations of exclusive patent rights in a wide variety of countries to determine the extent such limitations may play a role in providing access to patented medicines, other medical or biological products, and methods of medical treatment of patients, so as to facilitate health care, notably in the context of public health crises. AIPPI, through its Resolution Q202 (*see* Appendix at A5, Resolution Para. 5), encourages all member countries to allow medical personnel the freedom to provide medical treatment of patients without the authorization of any patentee, at least under certain circumstances discussed further below.

In the overwhelming super-majority of countries (indeed, in all 33 countries studied by AIPPI other than the United States and Australia), the societal objective of allowing medical treatment of patients to be unfettered by exclusive patent rights is achieved by excluding methods of medical treatment of patients from patent eligibility altogether. In the United States, this objective is supposed to be achieved by a statutory scheme eliminating, more or less, the availability of cer-

tain provisions of the Patent Laws with respect to certain types of potential actions against certain defined sets of individuals and entities. *See generally* 35 U.S.C. § 287(c).

Thus, while the question presented asks whether such claims fall within the ambit of patentable subject matter under 35 U.S.C. § 101, any such inquiry may be unnecessary and, as a matter of law, is prohibited if the district court lacked subject matter jurisdiction over the action. *See* Rule 12(h)(3), Fed. R. Civ. P.

For reasons that are not clear, Congress' legislative effort to achieve a globally-desired limitation of exclusive patent rights, at least under certain circumstances, appears to have been unapplied, misapplied, or simply overlooked by the district court and the Court of Appeals for the Federal Circuit in this case. AIPPI urges this Court to apply the statutory scheme eliminating entirely this patent dispute (and the attendant costs to society, the medical profession, and patients themselves) involving medical treatment of patients.

IV. ARGUMENT

AIPPI's Resolution Q202 ("The impact of public health issues on exclusive patent rights"), adopted at the Boston Congress, September 6-11, 2008, states (Appendix at A5, Resolution Paragraph 5):

> To the extent that the patent law permits patentability of methods of medical treatment, the law should provide for an exception to the rights of a patentee, allowing medical personnel to use

> patented methods of medical treatment, without the authorisation of the patentee, in circumstances where it is not practicable to negotiate a licence before treatment.

AIPPI did not study the issue of patent eligibility of methods of medical treatment of patients, *per se*. However, such study was not necessary, as only two of the countries' laws studied allowed for such patent eligibility at all (those two countries being Australia and the United States).[2] In the realm of public health issues, notably in the context of public health crises, it was resolved that a nation's patent laws should not impede or impair access to medical treatment, at least under certain circumstances. Given the state of the laws around the world, it should be understood that Resolution Q202 confirms the current situation in most countries, even including the United States, at least in theory.[3]

In *Laboratory Corp. of America Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006), a prior case presenting essentially the same question as is presented in this case, and in which certiorari had been granted but then dismissed as having

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[2] *See* AIPPI Summary Report, Question Q202 attached hereto (Appendix at A6-A42), Sec. (I)(5), at A16.

[3] At the time AIPPI Resolution Q202 was adopted, Australia was the only studied country in which methods of medical treatment were eligible for patenting and in which there was no defense, exclusion or exemption of any kind from liability for patent infringement resulting from the practice of such methods. *See* AIPPI Summary Report, Question Q202, Sec. (I)(5), Appendix at A16, and discussion of "Medical treatment defence," Appendix at A34.

been improvidently granted, Justices Breyer, Stevens, and Souter wrote that "special public interest considerations" are implicated by the question of patent eligibility for methods of medical treatment of patients because allowing such patents would "inhibit doctors from using their best medical judgment," would "force doctors to spend unnecessary time and energy to enter into license agreements," and would "divert resources" from healthcare tasks to "the legal task of searching patent files," among other deleterious effects. *Id.* at 135. These are the very same concerns addressed in AIPPI Resolution Q202. At minimum, there is a recognized danger, or at least special undesirability, of requiring doctors to negotiate and obtain patent licenses in order to treat patients, at least when "not practicable" to do so before treatment.

It is difficult to imagine many circumstances in which it would be "practicable" for a physician to identify the need for, seek and then successfully obtain a patent license before ordering optimization of a course of drug administration to a patient. In this case, a method of dosage optimization for a specific patient, by that patient's physician, is precisely what is claimed in the patent-in-suit. Respondent has previously argued that the "entire purpose of these inventions is to improve a process of patient treatment. *There are, in fact, no uses of the claimed processes other than in connection with patient treatment.*" (*See Prometheus Labs., Inc. v. Mayo Collaborative Servs. (dba Mayo Medical Labs)*, Appeal No. 2008-1403, Appellant's Reply Brief dated April 24, 2009, at 14 (Fed. Cir.) (emphasis added). Thus,

the "special public interest considerations" previously recognized by this Court are precisely implicated here.

Under current U.S. law, the provisions of 35 U.S.C. § 287(c)(1) of the Patent Act eliminate the availability of 35 U.S.C. § 281 (remedy by civil action), § 283 (injunction), § 284 (damages), and § 285 (attorney fees) against both the "medical practitioner" and "related health care entity" (defined as including but not limited to nursing home, hospital, university, medical school, health maintenance organization, group medical practice, or a medical clinic), at least as to a "medical activity," defined as "the performance of a medical or surgical procedure on a body." Thus, when Section 287(c)(1) applies, the courts lack subject matter jurisdiction to hear a specified class of claims of patent infringement against specified classes of potential infringers.

By enacting Section 287(c)(1), Congress has pronounced that at least some medical activities should be outside of, and free from interference by, the patent system. AIPPI respectfully suggests that both the infringement claims at issue and the named defendants in this case fall within those specified classes.

The definition of "medical activity" to which the exemption of § 287(c)(1) applies contains three exceptions codified in Section 287(c)(2)(A), but none of them applies here. It is indisputable that neither Section 287(c)(2)(A)(i) ("use of a patented machine, manufacture, or composition of matter") nor Section 287(c)(2)(A)(iii) (practice of process in violation of a biotechnology patent) applies. Similarly, while Section 287(c)(2)(A)(ii) removes "the

practice of a patented use of a composition of matter" from the exemption, the claims at issue in this case do not fall within this exemption.

U.S. Patent No. 6,355,623, "Method of treating IBD/Crohn's disease and related conditions wherein drug metabolite levels in host blood cells determine subsequent dosage" (hereinafter "the '623 patent"), describes a method of improving the treatment of autoimmune diseases by providing physicians a way to "individually calibrate a patient's dosage [of a particular medication] without having to take a wait-and-see approach." Brief for the Respondent in Opposition (to the petition for writ of certiorari), at 4. First, at least one asserted claim, i.e., claim 46, of the '623 patent recites only "determining" a patient's metabolite levels. (It is apparent that such "determining" requires withdrawal of a certain amount of the patient's blood, without question a "medical activity.") Second, as Respondent argues, the asserted patent claims are not drawn to the use of a composition of matter but instead are "processes to generate useful treatment information for physicians." Brief for the Respondent in Opposition (to the petition for writ of certiorari), at 12. Instead of requiring that the drug dosage be increased or decreased based on metabolite levels found in the patient's blood, the claims simply "indicate a need" to adjust the dosage. *See* Petition for a Writ of Certiorari, at 6-7 ("Importantly, Prometheus's claims do *not* recite what is to be done once the physician mentally recognizes the correlation.").

In addition to immunizing the allegedly infringing activity from suit, Section 287(c) also frees certain classes of defendants in an infringement suit,

Petitioners here, from liability. The evidence of infringement presented by Respondent Prometheus centered on the patient treatment activities of Dr. Rokea A. el-Azhary, M.D., Ph.D., a clinical dermatologist working in the Dermatology Department at Mayo Clinic Rochester, who is unquestionably a "medical practitioner" entitled to the protection of 35 U.S.C. § 287(c)(1). That evidence concerned blood tests ordered by Dr. el-Azhary from the Biochemical Genetics Laboratory of Mayo Clinic Rochester.[4] Mayo Clinic Rochester is unquestionably a "related health care entity" with respect to Dr. el-Azhary, and is also entitled to the immunity from suit provided by 35 U.S.C. § 287(c)(1). Prometheus argues in passing that while "individual doctors generally are immune from suit, . . . the commercial entities that enable and induce the infringement (such as Mayo's for-profit laboratory) are not." *See* Brief for the Respondent in Opposition (to the petition for writ of certiorari), at 34. However, 35 U.S.C. § 287(c) makes no distinction between "for-profit," "not-for-profit," and any other types of the defined "related health care entities" based upon financial motivation or any other criteria, for that matter; all are immune from suit unless one of the three § 287(c)(2)(A) exceptions applies. There does not appear to be any reason to conclude that Mayo Clinic Rochester and its related Mayo Collaborative Services are not "related health care entities" within the meaning of 35 U.S.C. § 287(c)(2)(C) and

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[4] It is understood that the Biochemical Genetics Laboratory at Mayo Clinic Rochester is actually part of Petitioner Mayo Collaborative Services, strictly as a matter of corporate organization.

(D), both entitled to be free from patent infringement suits of the instant type.

Thus, it appears that both named defendants are plainly "related health care entities" and that, accordingly, Congress has eliminated availability of a federal civil action for patent infringement of Prometheus' patent against them. The immunity from suit provided by Congress in 35 U.S.C. § 287(c)(1) should be given effect, and the case should be dismissed for lack of federal subject matter jurisdiction. That this issue apparently was not raised before either the district court or the Federal Circuit is of no import, as it is hornbook law that "[o]bjections to subject-matter jurisdiction . . . may be raised at any time." *Henderson v. Shinseki*, 562 U.S. __, __, 131 S. Ct. 1197, 1202 (2011).

Dismissal of this action for lack of federal subject matter jurisdiction comports with the letter and spirit of AIPPI Resolution Q202, which states that medical personnel should not be constrained by patent rights in circumstances where it "not practicable to negotiate a licence before treatment." Given the nature of the patent claims in this case and the types of defendants against whom the assertions of infringement have been made, allowance of the infringement action would either: (a) require a hospital laboratory such as the Biochemical Genetics Laboratory at Mayo Clinic Rochester to identify, obtain, and maintain a complete library of patent licenses covering every test that any doctor at Mayo Clinic Rochester might ever order, or (b) require the hospital laboratory to itself order a patent infringement search and study each time a Mayo Clinic

doctor orders a diagnostic blood test, and then obtain a license when deemed necessary or advisable in the opinion of Mayo Clinic Rochester's qualified patent counsel. Because neither of these options is "practicable," application of Congress' legislative solution in 35 U.S.C. § 287(c)(1) is appropriate and would achieve the purpose of AIPPI Resolution Q202.

V. CONCLUSION

The U.S. Congress has chosen to implement a public policy nearly deemed universally desirable, namely, freedom of doctors and their related facilities from patent infringement concerns, by eliminating availability of federal civil actions in certain defined circumstances. AIPPI, through its Resolution Q202, supports this public policy for at least the "special public interest considerations" previously recognized by Justices Breyer, Stevens, and Souter. This case appears to fall squarely within the statutory immunity from patent suit under 35 U.S.C. Sec. 287(c)(1), yet this seemingly critical issue does not appear to have been briefed, or even seriously raised, at any stage of the proceedings below. AIPPI respectfully submits that in view of Congress' withdrawal of the remedy by civil action in cases such as this one, federal subject matter jurisdiction is lacking, and that the case should be dismissed on this basis.

Respectfully submitted,

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APPENDIX

A1

[LETTERHEAD OF AIPPI]

Resolution

Question Q202

The impact of public health issues on exclusive patent rights

Yearbook 2008/I, pages 367-369
Congress Boston, 6-11 September 2008

AIPPI

Noting that:

1) The focus of this resolution is exceptions to exclusive patent rights applicable to medicines and other medical products.

2) Access to affordable medicines and other medical products is a pressing issue but exceptions to exclusive patent rights alone cannot resolve this issue.

3) AIPPI has studied exceptions to exclusive patent rights in previous questions, leading in particular to:

   i) The resolution of the Executive Committee of Barcelona in 1990—Question Q101, Yearbook 1991/I, page 298 entitled 'Parallel Import Of Patented Products' *(Barcelona Parallel import Resolution);*

   ii) The resolution of the Executive Committee of Tokyo in 1992—Question Q105, Yearbook 1992/III, pages 282-283

entitled 'Experimental Use as a Defence to a Claim of Patent Infringement' (*Tokyo Experimental Use Resolution*); and

iii) The resolution of the 38th Congress of Melbourne in 2001—Question Q156, Yearbook 2001/I, pages 511-512 entitled 'International Exhaustion of Industrial Properly Rights' (*Melbourne International Exhaustion Resolution*).

4) The Barcelona Parallel Import Resolution resolved that a patentee be able to invoke its patent against parallel import of a patented product, notwithstanding the circumstances under which such product has first been put on the market in a given country "B", subject to exception by contractual agreement authorising import into another country "A".

5) Paragraph 3 of the Tokyo Experimental Use Resolution resolved that each country should except acts done for experimental purposes from the rights of the patentee on the basis that experimental use:

i) Includes any use of the patented invention performed for academic purposes and having no commercial nature;

ii) Includes testing to evaluate the teaching of the patent and validity of the patent;

iii) Includes any use of the patented invention to an extent appropriate to experimentation (as opposed to commercial use) which is for the purpose of improv-

ing the invention or making an advance over the invention or finding an alternative to the invention, but not the commercial exploitation of the subject of any improvement or advance; and

iv) Should be subject to the overriding principle that the use must involve work on the subject of the patent; use merely to obtain the advantage of the invention disclosed by the patent is not experimental use.

6) The Melbourne International Exhaustion Resolution affirmed the Barcelona Parallel Import Resolution and resolved that there should be no international exhaustion of industrial properly rights (patents, trademarks, designs and plant breeder's rights) notwithstanding that regional exhaustion may be applied in order to foster regional integration of different national economies under a uniform regulatory and legal framework.

7) The patent law in some countries provides for an exception to exclusive patent rights for on "extemporaneous" preparation of a medicine in a pharmacy For individual cases in accordance with a medical prescription issued by a medical doctor (commonly referred to as the individual prescriptions exception).

8) A number of WTO Members have not yet ratified Article 31bis of the TRIPs.

Considering that:

1) **Patent law provides for a number of exceptions to exclusive patent rights which may play a role in providing access to patented medicines and other medical products.**

2) **Compulsory licensing is a more appropriate and proportionate means of providing access to patented medicines and other medical products than expropriation of patent rights.**

Resolves that:

1.1) **Patent law should provide for an exception to the rights of a patentee, allowing a party to undertake, without the authorisation of the patentee, experiments relating to the subject-matter of the invention, irrespective of whether the ultimate aim of the experiments may be commercial.**

1.2) **Paragraph 3 of the Tokyo Experimental Use Resolution is affirmed insofar as it is not in conflict with paragraph 1.1.**

2) **Patent law should provide for an exception to the rights of a patentee, allowing a party to undertake, without the authorisation of the patentee, acts necessary for the purpose of obtaining regulatory approval for medicines and other medical products such as medical devices, diagnostics, research tools and the like.**

3) **The Barcelona Parallel Import Resolution and the Melbourne International Exhaustion Resolution are each affirmed.**

4) To the extent that the patent law provides for an individual prescriptions exception, the exception should be limited to preparation of medicines as and when required for an individual patient and should not extend to situations where medicines are prepared on a larger scale.

5) To the extent that the patent law permits patentability of methods of medical treatment, the law should provide for an exception to the rights of a patentee, allowing medical personnel to use patented methods of medical treatment, without the authorisation of the patentee, in circumstances where it is not practicable to negotiate a licence before treatment.

6) Concerning public health:

   a) the patent law should provide that a compulsory license can only be granted in exceptional and strictly defined circumstances.

   b) the law should not permit expropriation of patent rights.

7) Article 31bis of the TRIPS should be promptly ratified by WTO Members that have not yet done so.

[LETTERHEAD OF AIPPI]

Summary Report

Question Q202

The impact of public health issues on exclusive patent rights

This Question considers the limitations of exclusive patent rights in a wide variety of countries. Its particular focus is limitations which may play a role in providing access to patented medicines and other medical or biological products so as to facilitate health care, notably in the context of public health crises.

The Reporter General has received 33 Group Reports from the following countries (in alphabetical order): Argentina, Australia, Belgium, Brazil, Bulgaria, China, Columbia, Denmark, Ecuador, Egypt, Estonia, Finland, France, Germany, Ireland, Italy, Japan, Malaysia, Mexico, the Netherlands, Norway, Peru, Philippines, Portugal, Republic of Korea, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, United Kingdom and United Slates of America.

The Reports provide a comprehensive review of the limitations imposed an exclusive patent rights under national patent laws. This Summary Report cannot attempt to reproduce the detailed rules explained by each Group or carefully selected examples used to illustrate those rules in practice. It may also be the case that particular words and phrases which have a specific meaning in their

original language cannot be translated fully. If any doubt exists as to the exact position in a particular jurisdiction, reference should be made to the original Group Reports.

I) Analysis of current law and case law

1) *Is a research or experimental use exception recognised under your patent law? If so, under which conditions? What is the scope of the research exception? Specifically, is research or experimental use permitted for commercial purposes?*

The vast majority of the Groups reported that a research or experimental use exception was recognised in their jurisdiction (either through statutory measures or doctrine and jurisprudence). In these jurisdictions an otherwise infringing act will not infringe if it is done for experimental purposes relating to the subject matter of the invention.

The patent laws generally do not give a definition of "experimental" but it is recognised that an act is an experiment if it seeks to generate genuinely new information (and not if it seeks simply to verily existing knowledge). The UK Group Report quoted the Court of Appeal in ***Monsanto v Stauffer*** where it was observed that experiments are "trials carried out in order to discover something unknown, or to test a hypothesis, or even in order to find out whether something which is known to work in specific conditions . . . will work in different conditions".

A number of Group Reports (Belgium, Denmark, Finland, Germany, Sweden, Switzerland, UK) note that this does not rule out an ultimate commercial aim, so long as the trials are experiments. In these jurisdictions experimental use is not only permitted for a purely scientific purpose, but also for mixed scientific and commercial purposes.

On the other hand, trials to demonstrate to a third party (e.g. a regulator) that a product works as its maker claims are not "experiments", according to the UK Group Report.

The German Group Report emphasises that the experimental use exception is limited in that experiments will only be deemed permissible if they use the patented subject matter as the object of the test and not merely as a means of realisation. Moreover, experiments which are conducted to clarify economic factors, such as market demand, price acceptability or distribution possibilities are not permissible. The German and Dutch Group Reports point out that experiments may only be carried out to an extent justifying the experimental purpose; clinical trials that take place on a very large scale do not fall under the research exception.

In a number of countries (Argentina, Brazil, Ecuador, France, Italy, Malaysia, the Philippines), research and experimental use are only permitted for a purely scientific purpose, but not a commercial purpose. Similarly, in the United Slates, the research exception is limited to narrowly non-commercial uses such as "gratifying a philosophical taste, or

curiosity, or for mere amusement". The exception does not even extend to pure scientific research if research is the infringer's business.

Turkey and the Republic of Korea provide for a research or experimental use exception, but it is not clear whether experimental use is permitted for commercial purposes.

In Thailand experimental use for a commercial purpose is permitted provided that it does not unreasonably conflict with a normal exploitation of the patent and does not unreasonably prejudice the legitimate interests of the patent holder. The Thai Group Report does not specify what this proviso means.

In Australia and South Africa, there is no express provision to provide for a research or experimental use exception from infringement. In the South African case of Monsanto v Stauffer the High Court stated that even experimental use will amount to infringement if the experiment uses the patented invention. The use of the patent to prepare for marketing registration of its own similar product was, therefore, found to constitute infringement. In Australia, researchers tend to act on the assumption that a research exception exists, but in the absence of Australian court authority, it is not clear what the conditions are in which the exception would operate or what the scope of the exception would be.

2) *Is a Bolar-type exception recognised under your patent law? If so, under which conditions? What is the scope of the Bolar exception? Specifically, is it limited to drugs or does it also apply to other products, including biological products, research tools, etc.? If your patent law does not provide for a Baler exception, will using an invention without the patentee's consent for the purpose of obtaining approval of a generic product be covered by the research exception?*

The European Union (EU) introduced a Community-wide Bolar exemption under Directive 2004/27/EC (with respect to medicinal products for human use) and Directive 2004/28/EC (with respect to veterinary medicinal products) which were implemented by all member states on October 30, 2005. Therefore, all of the reporting Groups which ore member states of the European Union or the European Economic Area (EEA), respectively (Belgium, Bulgaria, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, United Kingdom) recognise a Bolar-type exception. This Bolar exemption applies to experimental activities carried out by generic manufacturers with a view to obtaining a marketing authorisation for a generic drug. These are essentially bioequivalence studies and such further studies as may be required to cater for any differences between the basic approved product and the "generic" or "biosimilar" product.

The Bolar exception is limited to human and veterinary medicinal products. The Dutch Group Report stales that research tools or medical devices would not be covered by this exception as these products will generally not meet the definition of medicinal product. Conversely, the Swedish Group reports that the Bolar exception would include biological products if these are to be considered as reference medicinal products, and the use of research tools would be covered by the exception if they are substantially related to the reference medicinal product.

The Irish Group report notes that the Bolar exemption does not entitle innovative companies to make experimental uses of patented medicines or research tools for the purpose of seeking a marketing authorisation for a new medicinal product. On the other hand, in Denmark, France and Germany the Baler exception is not limited to acts directed at obtaining market approval of a generic, but rather encompasses market approval of innovative drugs as well.

A Bolar-type exception is also recognised in most other jurisdictions (Argentina, Australia, Brazil, Malaysia, South Africa, Switzerland, Thailand, Turkey, United States).

In the United States, the Bolar exception is broadly applied to pre-clinical testing of drugs or potential drugs "al least as long as there is a reasonable basis to believe that the compound tested could be the subject of . . . and the experiments will produce the types of

information relevant to" an application for approval for clinical trials or marketing (*Merck KGaA v Integra Lifesciences*). The Bolar exception is limited to drugs for human use; other biological products would only be covered to the extent that they are regulated as drugs. The exception does not apply if the drug is primarily manufactured using recombinant DNA or hybridoma technology or if the drug is a new animal drug or veterinary biological product.

The Australian and Thai Group Reports note that the Bolar exception is limited to drugs; other products such as biological products, medical devices, and research tools are excluded from the exception.

In Argentina, Brazil, Malaysia, and South Africa, the Bolar-type exception is not limited to pharmaceutical products; it applies to any other product requiring regulatory approval. This would for example not only cover pharmaceutical, but also agrochemical products which require marketing authorisations before such products may be put on the market. The Brazilian and Malaysian Group Reports state that biological tools and research tools would also be covered by this exception. The Swiss Group is of the opinion that biological products would also be covered to the extent they require regulatory approval; however, medical devices and research tools do not seem to be exempted.

In Ecuador, Japan and the Republic of Korea, no Bolar-type exception is recognised under the patent lows. However, in Ecuador and in

Japan, clinical trials and other acts seeking to obtain approval of a generic product are exempted under the research exception. Also in the Republic of Korea, researchers tend to act on the assumption that using an invention without the patentee's consent for the purpose of obtaining approval of a generic product will be covered by the research exception; there is, however, no court authority.

In China, Columbia, Peru and the Philippines, a Bolar-type exception is not recognised and using an invention without the patentee's consent for the purpose of obtaining approval of a generic product will not be covered by the research exception. However, in Peru a Bolar-type exception will soon be recognised under the patent law since the Trade Promotion Agreement Peru-USA includes a Bolar-type exception. Similarly, in Chino and the Philippines it is expected that the law will soon be amended to provide for a Bolar-type exception.

3) *Are parallel imports of patented medicines, medical devices or similar permitted? If so, under which conditions? Do the same principles apply if the products originate from markets where they were made available under a compulsory license?*

Within the EEA, regional exhaustion applies, i.e. a patented product, put on the market anywhere in the EEA by the patentee or with his consent, is free to move anywhere in the EEA. However, parallel imports of patented medicines, medical devices or similar from outside the EEA are not permitted.

In most other countries, only national exhaustion of rights applies and parallel imports of patented medicines, medical devices or similar from outside the country are generally not permitted (Brazil, China, the Philippines, South Africa, Switzerland, Turkey, United States).

In Argentina, Columbia, Ecuador, Egypt and Peru, international exhaustion of patent rights applies; as a result, parallel imports of patented medicines, medical devices or similar are permitted.

In Australia and Japan, parallel importation is only permissible to the extent the patentee has not made it a condition of sale that the purchaser may not import their goods into Australia and Japan.

In South Africa, even though national exhaustion applies, the parallel importation of patented medicines has specifically been provided for by an amendment of the South African Medicines and Related Substances Act. According to this amendment, the Minister may, based on Article 8 of TRIPS, prescribe conditions for the supply of more affordable medicines so as to protect the health of the public, and in particular may determine that the patent rights shall not extend to acts in respect of medicines which have been put on the market.

The principle of exhaustion does not apply if the products were put on the market under a compulsory license, the reason being that they were not made available "by the patentee

or with his consent". This is the general view in Europe, in accordance with ECJ 9 July 1985, C-19/84 *Pharmon v. Hoechst*. This is also the view in Egypt, Japan and Malaysia, but not in the Republic of Korea where the patent rights are exhausted even if the products were put on the market under a compulsory license.

4) *Is an individual prescriptions exception recognised under your patent law? If so, under which conditions?*

An individual prescriptions exception is recognised under the patent laws of Argentina, Belgium, Brazil, Bulgaria, Denmark, Finland, France, Germany, Italy, Japan, Philippines, Republic of Korea, Spain, Sweden, Thailand, Turkey, and UK.

The patent laws in these countries provide that no infringement arises where there is an extemporaneous preparation of a medicine in a pharmacy for individual cases where such is in accordance with a medical prescription issued by a registered medical practitioner. The German and Swedish Group Reports state that this exemption does not allow stockpiling of pharmaceuticals in a pharmacy. Rather, a doctor's prescription for one single patient is required on the basis of which the medicine is prepared in the pharmacy.

An individual prescriptions exception is not recognised under the patent laws of Australia, Peru, Ecuador, Egypt, Estonia, Malaysia, Mexico. Netherlands, Peru, South Africa, Switzerland, and United States.

5) *Please answer this question only if in your country methods of medical treatment are patentable subject matter: Does your patent law provide for a medical treatment defence or similar exception to the patentee's exclusive rights?*

Methods of medical treatment are only patentable subject matter in Australia and in the United Stales. In all other reporting countries methods of medical treatment are not patentable.

Australian patent law does not provide for a medical treatment defence or similar exception to the patentee's rights. One Australian case (*Bristol-Myers Squibb & Co. v FH Faulding & Co. Ltd.)* suggested that medical practitioners who wish to use patented methods of medical treatment should seek a compulsory license.

In the United States where a medical practitioner performs a medical activity that infringes or actively induces infringement of a patent, the medical practitioner and related healthcare entity (hospital, clinic, medical school, etc.) are exempt from suit for infringement. The exemption extends to the performance of methods of medical treatment, but not to the use of a patented product.

6) *Are compulsory licenses available under your patent law? If so, under which conditions and on which grounds (e.g. to remedy anticompetitive conduct, for cases of emergency, other public interest grounds, etc.)? Are you aware of any compulsory licenses granted in your*

country for the domestic manufacture and supply of pharmaceutical products? If so, please provide details, including the name of the licensor, the licensee and the product covered.

Compulsory licenses are available under the patent laws of all reporting countries.

The general requirements of Art. 31 TRIPS are applicable in all reporting countries. For instance, as a general rule, a person may only apply for a compulsory licence under the patent provided he has made efforts to obtain a license from the proprietor on reasonable commercial terms and conditions and his efforts have not been successful within a reasonable period. In accordance with TRIPS, this requirement may be waived by a Member in the case of national emergency or other circumstances of extreme urgency or in cases of public non-commercial use, as pointed out by the Philippine Group. In situations of national emergency or other circumstances of extreme urgency, the right holder shall, nevertheless, be notified as soon as reasonably practicable.

Compulsory licenses are available on a number of grounds. Generally speaking, the following grounds are available:

> In most reporting countries (Argentina, Belgium, Brazil, Columbia, Denmark, Ecuador, Egypt, Estonia, Finland, France, Italy, Japan, Malaysia, Mexico, Netherlands, Peru, Portugal, Philippines, Republic of Korea, Spain, Sweden, Thailand, Turkey), a compulsory license may

be applied for on the ground of failure to work or insufficient working.

The Argentine, Mexican and Philippine Group Reports point out that importation of the product embodying the invention is deemed to be sufficient working of the patent.

Compulsory licenses are not granted if the patent owner is able to give valid reasons for their failure to work the invention, e.g. if the inactivity derived from a force majeure event, including objective difficulties in obtaining market approval before a regulatory authority. This is specifically stated in the Group Reports of Argentina, Brazil, Columbia, Ecuador, Japan, Malaysia, Mexico, Peru, Philippines, Thailand, and Turkey.

In accordance with Article 5 (A) (4) Paris Convention, a compulsory license may not be applied for on the ground of failure to work or insufficient working before the expiration of a period of four years from the date of filing of the patent application or three years from the date of the grant of the patent, whichever period expires last. This is specifically stated in the Group Reports of Argentina, Australia, Belgium, Bulgaria, Denmark, Egypt, France, Japan, Sweden, Thailand, and UK.

The Belgian and Mexican Group Reports state that the applicant must have the

necessary means to undertake effective and continuous manufacturing in accordance with the patented invention.

The Danish, Italian and Spanish Group Reports note that working of the invention within the EEA or in a WTO country is considered working in the respective country.

In the vast majority of the reporting countries (Argentina, Australia, Belgium, Brazil, Bulgaria, China, Columbia, Ecuador, Egypt, Estonia, Finland, France, Germany, Italy, Japan, Malaysia, Netherlands, Peru, Portugal, Republic of Korea, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, and UK) a compulsory license may be applied for in the case of dependency, i.e. if the holder of a second patent covering an improvement on an invention that has already been patented by a third party may not practice its invention without authorization by the holder of the prior (first) patent. In accordance with Art. 31 (I) TRIPS agreement, in case of dependency the additional condition applies that the invention claimed in the second patent has to involve an important technical advance of considerable economic significance in relation to the invention claimed in the prior (first) patent.

In Estonia, the Netherlands, and Norway a compulsory license may also be

granted if it is necessary for using a granted plant breeder's right.

In most reporting countries (Argentina, Brazil, Bulgaria, China, Columbia, Denmark, Ecuador, Egypt, Estonia, Finland, France, Netherlands, Peru, Portugal, Philippines, Republic of Korea, Spain, Sweden, Switzerland, Thailand, and Turkey) a compulsory license may be applied for in the case of a national emergency or national security and/or based on other public interest grounds.

United States patent law also provides for the compulsory licensing of patents considered especially important to public welfare, i.e. patents related to "nuclear material or atomic energy" and patents that are necessary to enable a person to comply with the restrictions of the Clean Air Act.

Public health is expressly recognised as a public interest within the meaning of compulsory licensing provisions. This is expressly mentioned by the German, Japanese, and Portuguese Groups. Specifically, in Belgium and France a compulsory license may be applied for in the interest of public health for a medicine, a medical device, a product or medical device used for performing a diagnosis, the process necessary for the manufacture thereof, or a diagnosis method applied outside of the human or animal body. Some Groups (France,

Egypt, South Africa) specify that compulsory licenses may be granted in case the quantity and/or quality of patent protected medicines do not meet the public demand, if such medicines ore sold at excessive prices or in case of chronic, incurable or endemic diseases.

Malaysian law does not refer to the concept of compulsory licensing in relation to public interest, but allows the government to authorize a Government Agency or a third party designated by the government to use a patent without previous license. For instance, in October 2003, the Malaysian government authorised a Malaysian company to import anti-retroviral medicines used in the treatment of AIDS from Indian manufacturer CIPLA.

In some reporting countries (Argentina, Australia, Brazil, Columbia, Ecuador, Egypt, Germany, Italy, Philippines, Republic of Korea, Switzerland, UK, and United States) a compulsory license may be applied for to remedy a practice determined after judicial or administrative process to be anti-competitive. A similar concept applies in Malaysia although it is not referred to as compulsory licensing. The German Group emphasises that compulsory licenses on the basis of anti-trust law have a greater practical significance than compulsory licences on the basis of patent law. Notably, compulsory licenses under

anti-trust law are generally available in cases where the compliance with a general industry standard requires the use of a patent.

- In Switzerland compulsory licences are also available for research tools and diagnostic products.

In the United States, the broadest legal authority for the compulsory licensing of patents exists when patents are used by the federal government, limited only by a constitutional requirement of just compensation. In addition, some commentators in the United States have suggested that the Supreme Court's recent rejection of a general policy of granting permanent injunctions against patent infringers in eBay Inc. v. MercExchange creates a de facto compulsory license in favour of patent infringers who are willing to let the courts decide the appropriate licensing fee.

In Bulgaria, a granted compulsory licence will be revoked if the licensee does not start preparations for the use of the invention within one year after the grant of the compulsory licence. In Columbia, Ecuador, and Mexico the same rule applies, but two years after the grant of the compulsory license.

In the vast majority of the reporting countries no compulsory licenses have been granted.

In Brazil two compulsory licenses have been granted to the Brazilian Ministry of Health based on public interest grounds for the

importation of the anti-retroviral drug Efavirenz of Merck & Co. In addition, three compulsory licenses were granted for a Brazilian patent covering a process for manufacture of a vaccine against aftosa and one compulsory license was granted for a Brazilian patent of Monsanto Company.

In Denmark, in 1969 the Supreme Court granted a compulsory license to a Danish pharmaceutical company for a patent of Swiss Geigy AG regarding a process for manufacture of phenylbutazone on the ground of failure to work.

In Italy, the Competition Authority granted generic manufacturers compulsory licences to remedy an abuse of dominant position by Merck & Co.

In Portugal, a compulsory licence was granted to SAPEC AGRO for Portuguese patent no. 76,136 of Syngenta regarding a plant protection product.

In the Philippines, a total number of 6 compulsory licences have been granted, and in Thailand a total of 7 compulsory licenses have been granted. For more detailed information, including the name of the licensor, the licensee and the product covered, please refer to the respective Group Reports.

In the Republic of Korea, a total number of 6 compulsory licences have been applied for, but none granted so far.

7) *Has new Article 31bis TRIPS been ratified in your country? Are you aware of any other leg-*

islative amendment in your country with a view to implementing the WTO decision of August 30, 2003? Are you aware of any compulsory licenses granted in your country for the importation or exportation of pharmaceutical products? If so, please provide details, including the name of the licensor, the licensee and the product, if they are publicly available.

The majority of reporting countries have ratified and implemented Article 31bis TRIPS either directly (Australia, China, Japan, Mexico, Norway, Switzerland, UK, USA) or through the adoption of European Regulation 816/2006 on compulsory licensing of patents relating to the manufacture of pharmaceutical products for export to countries with public health problems (Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Netherlands, Portugal, Spain, Sweden, UK).

Argentina, Columbia, Ecuador, Egypt, Estonia, Malaysia, the Philippines, Thailand and Turkey have not yet ratified Article 31bis TRIPS or enacted any other legislative amendment with a view to implementing the WTO decision of August 30, 2003. Brazil has not ratified Article 31bis TRIPS, but enacted another legislative amendment with a view to implementing the WTO decision of August 30, 2003. Peru has not ratified Article 31bis TRIPS, but the Trade Promotion Agreement Peru-USA recognises the necessity of access to medicines in accordance with the WTO decision of August 30, 2003.

France, Switzerland, Sweden, and UK, among others, declared that they will not use the system as importing member for the purposes of Article 31bis TRIPS and its Annex.

In the vast majority of the reporting countries no compulsory licenses have been granted for the importation or exportation of pharmaceutical products.

In Brazil two compulsory licenses hove been granted to the Brazilian Ministry of Health for the importation of Efavirenz patented by Merck & Co.

8) *Is the government allowed to make use of a patented invention without previous license and if so, on what basis (e.g. crown use) and under which conditions?*

In most reporting countries the government is allowed to make use of a patented invention without previous license based on public interest grounds. For instance, in Brazil and in Thailand the government is allowed to make use of a patented invention without previous license in the case of a national emergency or national security. Similarly, in Finland, the Netherlands, and Norway the government is only allowed to make use of a patented invention without previous license in the case of war or national defence, respectively. In China, Germany, Ireland, Malaysia, the Netherlands, and the Philippines the government is required to compensate the patentee. The French Group notes that the government may rely on the Public Health Act to make use of a patented

invention in case of an emergency, notably an epidemic.

The United States government is allowed to make any use of patents without previous licenses, limited only by a constitutional requirement of just compensation. Similarly, in the UK any government department may make use of a patented invention without previous licence, limited only by the statutory requirement of reasonable compensation. Even the National Health Service's use of an invention has been deemed to be Crown use. Analogous rules regarding Crown use apply in Australia.

The South African and UK Groups point out that the State use and Crown use, of a patented invention in essence amount to compulsory licenses, although they are not "licenses" in law because State use and Crown use are deemed not to be an act of patent infringement.

The Swedish Group Report notes that the government may also apply for a compulsory licence.

The Argentine, Columbian, Ecuadorian, Estonian, Italian, Japanese, Mexican, Peruvian, Portuguese, Spanish, Swiss and Turkish Groups state that their governments are not allowed to make use of patents without previous licenses.

The Belgian and Danish Groups state that no such provision exists under their laws.

9) *Is the government allowed to expropriate a patent and, if so, under which conditions?*

In most reporting countries (Argentina, Brazil, Denmark, Egypt, Italy, Portugal, Spain, Switzerland, Sweden, USA) the governments are allowed to expropriate a patent, if the public interest requires so and the patentee is fully compensated. Similarly, in Finland, France, Norway, Sweden the government is only allowed to expropriate a patent in the case of war.

There have been no reported instances of the government expropriating a patent. The Swedish Group points out that in case of expropriation of a patent regarding national security, such expropriation would likely be kept confidential. The Danish Group stresses that expropriation is not necessary as compulsory licensing provides sufficient remedy.

The Bulgarian, Columbian, Chinese, Estonian, Japanese, Malaysian, Mexican and Turkish Groups state that their governments are not allowed to expropriate a patent.

The Belgian, Ecuadorian, Peruvian, Philippine, and South African Groups state that no such provision exists under their laws.

10) *If your patent law recognises other means of facilitating access to medicines, medical devices, diagnostics and the like, notably in the context of public health crises (including, among others, information tools such as the Orange Book providing timely consumer information on generic drug approvals),*

which have not been discussed above, please explain.

The Brazilian Group notes that patent applications for pharmaceutical products undergo a double examination in Brazil, one performed by the Brazilian Patent Office and one performed by the regulatory authority ANVISA for the purpose of taking into account public health policy grounds. For instance, ANVISA has rejected second medical use claims and patent applications relating to anti-HIV drugs to assure access to essential medicines.

The Bulgarian and Spanish Groups state that regulatory law rather than patent law facilitates access to medicines by waiving the requirement of marketing authorizations for pharmaceutical products in the case of epidemics, spreading of chemical agents or nuclear radiation. In addition, the Spanish Group Report notes that allowing the importation and use of medicines which are not approved in Spain, but necessary for the medical treatment, in essence amounts to facilitating access to medicines.

The Danish and French Groups point out that access to medicines is facilitated by the fact that the regulatory authorities may grant marketing authorizations for generics prior to expiry of the patent protection. The Danish, French, and Norwegian Groups note that their laws specifically facilitate access to generic drugs to the extent that they provide incentives for doctors to prescribe generic drugs (for instance, by providing for reim-

bursement by the health insurance for the cost of the generic only unless the doctor sets out medical grounds for prescribing the original product).

In this regard, United States Group refers to the Orange Book mentioned in the question which provides up to date information on generic drug approvals and is made available by the Food and Drug Administration in electronic form at http://www.fda.gov/cder/ob/default.htm. Similarly, in Norway, generic drug approvals are also accessible on the website of the Medicines Agency.

II) Proposals for adoption of uniform rules

1) Should patent law provide for

— *research and experimental use exception;*

— *Bolar exception;*

— *parallel import of patented medicines;*

— *individual prescriptions exception;*

— *medical treatment defence;*

— *compulsory licensing;*

— *expropriation;*

— *any other limitations of the exclusive patent rights to facilitate access to medicines, diagnostics, medical devices and the like?*

If so, under what circumstances? If not, why not?

Research and experimental use exception

The majority of Groups (Argentina, Australia, Belgium, Brazil, Bulgaria, China, Columbia, Denmark, Ecuador, Finland, Ireland, Italy, Mexico, Netherlands, Norway, Peru, Portugal, Republic of Korea, Spain, Sweden, Switzerland, Thailand, Turkey, UK) are in favour of a research and experimental use exception.

The Australian and Dutch Groups stress that legal clarification of the exception is required.

Some Groups (Argentina, Peru, Turkey) think that the experimental use exception should be strictly limited to cases involving non-commercial purposes. On the other hand, the Thai Group specifically states that the exception should not be limited to non-commercial purposes.

The Norwegian and UK Groups are of the opinion that this exception should be limited to experiments on the subject matter of the invention. The Swiss Group notes that the exception should not cover the use of a patented invention as a tool in research on other objects.

The Japanese Group does not think that the experimental use exception is required. In case the patent laws provide for such exception, the Japanese Group believes that resolution Q105 adopted in Tokyo in 1992 should be followed (with the exception of point 4). According to this resolution the experimental

use exception is supported by AIPPI and should essentially be limited to non-commercial purposes (the resolution mentions use of the patented invention for academic purposes having no commercial nature, testing to evaluate the leaching of the patent and validity of the patent, improving the invention or making an advance over the invention or finding an alternative to the invention, but not the commercial exploitation of the subject of any improvement or advance). The resolution further stresses that the use must involve work on the subject of the patent; use merely to obtain the advantage of the invention disclosed by the patent is not experimental use. AIPPI further resolved that the experimental use exception should be narrowly interpreted and the burden of proof should lie on the third party relying on the experimental use exception. Point 4 of the resolution Q105 (which, according to the Japanese Group, should not be followed) states that use by a party during patent life for the purpose of any regulatory approval to sell after patent expiry is not experimental use.

Bolar exception

The majority of Groups (Argentina, Australia, Belgium, Brazil, Bulgaria, China, Denmark, Ecuador, Finland, Germany, Ireland, Italy, Mexico, Netherlands, Peru, Portugal, Republic of Korea, Spain, Sweden, Switzerland, Thailand, Turkey, UK) is in favour of a Bolar exception. Some Groups (Denmark, Germany, UK) are of the opinion

that the Bolar exception should cover both generic and non-generic (innovative) drugs (e.g. selection inventions), but should only encompass such measures which are necessary to obtain market approval.

The Dutch Group thinks that the Bolar exception should apply to all products that require regulatory approval. The Thai Group thinks it should also cover biological products and research tools.

The Swedish Group thinks a Bolar exception is acceptable if it is balanced with a system of patent term extension. Similarly, the Ecuadorian Group stresses that the Bolar exception is only acceptable as long as generic manufacturers may not market the product prior to expiry of the patent. In this regard, the French group thinks that there should be an efficient legal remedy for patentees to prevent the marketing of generics prior to expiry of the patents.

The Japanese Group again does not think that this exception is required, but in case it is deemed to be required, it should be covered by the experimental use exception. Conversely, the Swiss Group takes the view that the Bolar exception should go beyond the general research exception and allow the use of patented inventions in bioequivalence studies, batch validation and the like. It should, however, not allow stock-piling and preparation for large-scale manufacturing.

The Columbian Group is against a Bolar exception.

Parallel import of patented medicines

The majority of Groups (Argentina, Denmark, Finland, Germany, Ireland, Italy, Norway Japan, Netherlands, Sweden, Switzerland, Turkey, UK) is against international exhaustion and parallel import of patented medicines. The Japanese and UK Groups think that AIPPI should reconfirm resolution Q101 (adopted in Melbourne in 2001) which rejected international exhaustion.

Most European Groups (Denmark, Finland, Germany, Ireland, Italy, Norway, Sweden, as well as Turkey) think that regional exhaustion in homogenous economic areas such as the EEA is acceptable.

Some Groups (Brazil, Bulgaria, China, Columbia, Ecuador, Mexico, Peru, Thailand) are in favour of parallel import. The Ecuadorian Group stresses that any developing country should be entitled to have access to medicines at the best possible price.

The Australian Group thinks that parallel imports could increase access to patented medicines and does not unreasonably dilute the rights of the patentee.

Individuals prescriptions exception

Most Groups (Argentina, Belgium, Brazil, Bulgaria, China, Finland, Ireland, Italy, Japan, Mexico, Norway, Portugal, Republic of Korea, Sweden, Thailand, Turkey) are in favour of an individual prescriptions exception. Some Groups (Australia, Ecuador) think that the exception may be appropriate for

one-off, non-commercial prescriptions in cases of patient need, but agree that situations should be avoided where medicines are prepared on a large scale basis.

The Dutch, German, Swiss and UK Groups think that this exception has no relevance in practice and, therefore, do not see the need for it.

Medical treatment defence

Some Groups (Argentina, Belgium, Brazil, China, Columbia, Japan, Mexico, Norway) are in favour of a medical treatment defence, insofar as there is a need for such exception.

The Australian Group (which is the only reporting country where—besides the United States—methods for medical treatment are patentable) is of the view that in a commercial context it is unlikely that a medical practitioner would be sued and that, therefore, an explicit defence is unnecessary.

Some Groups (Bulgaria, Ecuador, Ireland, Sweden, Turkey) think that methods for medical treatment should remain non patentable.

Compulsory licensing

Most Groups (Argentina, Belgium, Brazil, Bulgaria, China, Columbia, Denmark, Ecuador, Finland, Ireland, Italy, Japan, Mexico, Netherlands, Norway, Portugal, Republic of Korea, Sweden, Switzerland, Thailand, Turkey, UK) are in favour of compulsory licensing under the current regime.

Some Groups (Australia, Germany) are critical because of the long lead times for the production of medicines. In the context of a pandemic, it may be that more than one licensee is required to provide sufficient product.

Some Groups (Argentina, Bulgaria, Sweden, UK) emphasize that compulsory licensing should be narrowly construed. The Swedish Group notes that extensive interpretation of Article 31(1) TRIPS "national emergency or other circumstances of extreme urgency" would erode the patent system to an extent where incentives for R&D might be weakened.

The Japanese Group thinks that AIPPI should reconfirm resolution Q187 (Limitations on exclusive IP Rights by competition law) adopted in Berlin in 2005. This resolution does not specifically mention compulsory licensing, but makes it clear that if the exercise of IP rights contravenes competition law, then the law should allow for the necessary remedies.

Expropriation

Only few Groups (Argentina, Australia, Brazil, China, Thailand) are in favour of expropriation.

Some Groups (Finland, Mexico, Philippines, Sweden, Turkey) take the view that expropriation should only be allowed in very exceptional circumstances.

Many Groups (Belgium, Columbia, Ecuador, Germany, Norway, Switzerland) think that compulsory licensing is adequate to address public health concerns and that expropriation is disproportionate and unnecessary. Additional Groups (Bulgaria, Japan, Netherlands, UK) are also against expropriation.

The Argentinean Group stresses that the limitation should be narrowly construed. The Australian Group states that the government needs to justify any expropriation decision it makes.

Other limitations

No Group has suggested other limitations of the exclusive patent rights to facilitate access to medicines, diagnostics, and medical devices. The French Group stresses that there should not be additional limitations beyond those provided by TRIPS.

2) *Do you see other ways than by limitations of patent rights in which patent law might facilitate access to medicines, diagnostics, medical devices and the like?*

The South-African and Swiss Groups note that access to affordable medicine is not the only critical factor for ensuring effective treatment to poor people suffering from pandemic and endemic illnesses. Effective and accessible health care systems, improved living (sanitary and dietary) conditions and better education all play an important part. The Swiss and UK Groups further mention that most of the drugs classified by WHO as

essential drugs are either available off-patent or not patent protected, yet over a third of the world's population still has no access to these drugs.

The Argentinean and Ecuadorian Groups stress that governments and laws may facilitate access in other ways by limitation of patent rights, for instance by controlling (subsidizing) the prices of patented medicines.

The Korean Group stresses the importance of adopting information tools such as the Orange Book to facilitate access to medicines.

As to patent law, the Swiss Group is of the opinion that patents are not an obstacle to the access to medicines, but to the contrary stimulate research and ensure that new medicines are found and brought to the market. Similarly, the South African Group points out that unduly limiting the protection afforded by patent rights on its own will not necessarily provide a solution. The Norwegian Group is also of the opinion that a well-functioning patent system will in itself have the effect of facilitating access. The Dutch Group is also of the view that a better safeguarding of the patentee's rights will facilitate access. The Dutch Group even recommends the use of non-violation complaints against countries which, when applying compulsory licenses in the context of public health, strictly act in accordance with the rules, but de facto against the spirit of TRIPS. Furthermore, the Dutch Group proposes that additional measures (such as extension of

patent term, additional recognition of inventors) be introduced into patent law in order to compensate the disadvantageous consequences of the grant of compulsory licenses.

In the context of patent law, the South African Group further proposes that the following initiatives be considered: providing for incentives to encourage relevant R&D (e.g. innovation prize models), supporting relevant innovative activities (e.g. research on the basis of traditional remedies) and promoting effective and sustainable technology transfer. Similarly, the Swedish Group thinks that incentives for development of new products, based on market exclusivity for a limited lime should be considered. The Swedish Group makes reference to the orphan drug provisions adopted in the EU in this context. These provisions grant 10 years of market exclusivity in the EU in return for the development of orphan medical products, meaning that for 10 years no other company could obtain permission to market a similar drug. Orphan drugs are defined as drugs intended to alleviate rare diseases. Another example would be the pediatric exclusivity provisions adopted in the EU. In order to enhance the development of pediatric medicines these provisions offer a 6 months patent term extension to makers of pediatric medicines. Similar provisions exist in the US.

The German Group points out that exclusions from patentability (as in the case of methods for medical treatment) also serve to facilitate access to medicines and the like.

The Mexican Group notes that more stringent examination of patentability also facilitates access to the extent that unjustified patents are avoided.

3) *Should any of the limitations of patent rights, specifically the research and experimental use exception, Bolar exception, and individual prescriptions exception be harmonised? If so, how? If not, why not?*

Most Groups (Argentina, Australia, Bulgaria, Columbia, Denmark, Finland, Italy, Mexico, Norway, the Philippines, Republic of Korea, South Africa, Spain, Sweden, UK) are in favour of harmonizing limitations of patent rights.

Some Groups (Argentina, Philippines, Spain) think that harmonization should be achieved through WTO. The Spanish Group also mentions the SPLT as possible means of harmonization. The Australian Group suggests that AIPPI takes the lead in promoting harmonization efforts.

Some Groups (Belgium, Ecuador, Ireland, Switzerland) are specifically in favour of harmonizing the major exceptions, notably the research and experimental use exception and Bolar exception.

The German Group thinks it is more important to harmonize the effects of a patent rather than the exceptions.

The Irish Group is against harmonizing the rules governing parallel import as this involves complex economic issues. Further-

more, the Irish group thinks that harmonization of compulsory licensing at TRIPS level is sufficient.

Some Groups (Brazil, Portugal, Thailand) are against harmonizing limitations of patent rights. The Thai Group states that each country should have the freedom to stipulate the limitations of patent rights taking into account the public interests of the country. The Turkish Group does not think that harmonizing the limitations of patent law will be possible.

Conclusion

It appears from the Reports that patent law provides for a number of limitations which may play a role in providing access to patented medicines, diagnostics, medical devices and the like. Most of these limitations, including the research and experimental use exception, individual prescriptions exception, medical treatment defence, compulsory licensing provisions, and expropriation, facilitate access to new medical products *per se*, either on a short term or long term basis. Some limitations specifically seek to provide access to affordable medicines and the like, i.e. the parallel import of patented medicines as well as the Bolar exemption—to the extent that it only covers generic drugs. Finally, access to medical products may also be affected by the availability of sufficient supplies. Some of the limitations will also ensure access to adequate supplies, notably in the context of public health crises. These include above all the compulsory licensing provisions, and expropriation. Most Groups focussed on medicines

in their Reports, but depending on the circumstances diagnostics, medical devices, biological products and the like may be just as important.

It follows from the Group Reports that there is large consensus as to the necessity of a research and experimental use exception, but it needs to be debated in the Working Committee whether the Groups are in favour of a research and experimental use exception which does not rule out an ultimate commercial aim, so long as the trials are experiments. If so, Q105 (Experimental use as a defence to a claim of patent infringement) which was adopted in Tokyo in 1992 will have to be revisited. Similarly, the Groups generally support a Bolar exception, but it will have to be discussed in the Working Committee whether the Bolar exception should also cover non-generic (innovative) products and extend to all products that require regulatory approval. It may be that this is another area where harmonisation could be achieved. The parallel import of patented medicines does not seem to have support and resolution Q101 (rejecting international exhaustion) could, therefore, be reconfirmed. The individual prescriptions exception—to the extent it has any relevance in practice—appears to be generally accepted, provided medicines are not to be prepared on a large scale basis. It is not entirely clear whether there is sufficient support in the Group Reports for a statement saying that medical methods should remain non-patentable, but it appears from the Group Reports that to the extent medical methods are patentable, the law should provide for a medical treatment defence. It also follows from the Group Reports that not only the neces-

sity of compulsory licensing provisions is recognised, the Groups also seem to agree that they should generally be narrowly construed. Only few Groups are in favour of expropriation, but due to the inherent linkage to notional public policy principles this is unlikely an area where harmonisation could be achieved, except perhaps a resolution providing that expropriation should only be allowed in exceptional circumstances as determined by governments, given that compulsory licensing is the more adequate and proportionate means of providing access. Finally, the Working Committee will have to consider whether AIPPI should support initiatives which provide for incentives, including patent term extension and market exclusivity, for development of new medical products.

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IN THE
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,
Petitioners,
v.
PROMETHEUS LABORATORIES, INC.
Respondent.

On Writ of Certiorari to the United States Court of Appeals For the Federal Circuit

BRIEF OF AMICUS CURIAE ASSOCIATION OF UNIVERSITY TECHNOLOGY MANAGERS IN SUPPORT OF RESPONDENT

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STATEMENT OF INTEREST

This brief is submitted by the Association of University Technology Managers ("AUTM") as *amicus curiae* in support of Respondent to urge the Court to affirm the judgment of the court of appeals, thereby rejecting the efforts of Petitioners and certain *amici* improperly to narrow the scope of patent eligibility under 35 U.S.C. § 101.[1]

The issues raised in this case are of great importance to AUTM's members whose central mission is to ensure that basic, early-stage scientific research is translated into commercial products for the public benefit.

AUTM was founded in 1974 as a non-profit professional association with the objective of addressing the concern that inventions funded by the United States government were not being commercialized effectively. Today, AUTM is the largest association of university technology transfer professionals, with a membership of more than 3,600 intellectual property managers and business executives from forty-five countries. AUTM's members represent more than 350 universities,

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[1] In accordance with Supreme Court Rule 37.3(a), counsel for all parties have consented to the filing of *amicus* briefs, and copies of the letters of general consent have been filed with the Clerk. Pursuant to Supreme Court Rule 37.6, AUTM states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than AUTM or its counsel.

research institutions, teaching hospitals, and government agencies worldwide, as well as hundreds of companies involved with managing and licensing innovations derived from academic and non-profit research.

AUTM has no interest in any party to this litigation or stake in the outcome of this case, other than its interest in seeking a correct, clear, and consistent interpretation of the United States patent laws in furtherance of AUTM's mission of advancing the field of technology transfer and enhancing the ability to bring academic and non-profit research to people around the world.

SUMMARY OF ARGUMENT

Congress intended that the threshold patent-eligibility standard set forth in § 101 of the Patent Act be construed broadly. Section 101 operates as a "coarse filter" to block at the outset only unpatentable laws of nature, natural phenomena, and abstract ideas, while allowing all other inventions and discoveries to be considered for patentability under the conditions set forth in other sections of the Patent Act. If a patent application describes a category of invention that is patent eligible, its patentability is then judged by the stringent requirements of §§ 102, 103, and 112, which protect against the issuance of patents for inventions and discoveries that lack novelty, are obvious in light of what is already known, or otherwise attempt to claim discoveries beyond what an inventor has invented and disclosed to the public. This framework encourages innovation in emerging—and even as yet unforeseen—fields of science and technology. AUTM urges this Court to reject Petitioners' short-sighted attempt to narrow the scope of patent-eligible subject matter under § 101.

Technology transfer ("tech transfer") licensing activity fuels innovation, particularly for biomedical technologies, but this success is dependent upon the clear, consistent, and correct interpretation of the patent laws, including § 101's patent-eligibility standard. The fundamental purpose of tech transfer is to translate academic research into practical application, and tech transfer relies on the patent system to operate effectively. Patent rights are the

currency of the tech transfer process, allowing early-stage research to be moved from universities and research institutions to the private sector for development and commercialization.

A broad, encompassing standard of patent eligibility, as intended by Congress and supported by this Court's precedent, is important to encourage innovative research and development, particularly in nascent biomedical fields like personalized medicine and established, but rapidly-evolving, fields like diagnostic testing. Eliminating entire categories of inventions and discoveries at § 101's eligibility threshold, as Petitioners urge, would reduce the number and diversity of inventions entering the product development pipeline and defeat Congress's intent to use the patent system to move discoveries from the research laboratory to the clinical setting.

Under this Court's controlling law, the Prometheus claims at issue in this appeal are clearly patent eligible under the broad standard of § 101. Any concerns about the patentability of the Prometheus claims, however legitimate they may be, are not properly addressed in this appeal. Whether the Prometheus claims meet the requirements for patentability is not before the Court and is irrelevant to the § 101 patent-eligibility determination. To ensure a vibrant system of technology transfer, extending from the research stage to practical application in the commercial market, the broad patent-eligibility standard of § 101 should not be conflated with the rigorous requirements for patentability set forth in §§ 102, 103, and 112.

ARGUMENT

I. THROUGH THE PATENT SYSTEM, UNIVERSITIES AND OTHER RESEARCH INSTITUTIONS ARE ABLE TO TRANSFER EARLY-STAGE RESEARCH TO THE PRIVATE SECTOR FOR FURTHER DEVELOPMENT AND COMMERCIALIZATION.

At its core, the function of the United States patent system is to drive innovation. This purpose is grounded in the U.S. Constitution, which provides that "The Congress shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art I, § 8, cl. 8. Congress used this power to create the U.S. patent system, codified at 35 U.S.C. §§ 1-376. Section 101 defines the inventions and discoveries eligible for patent protection:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

This Court has consistently recognized that "the language of § 101 is extremely broad." *J.E.M. Ag. Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130 (2001) (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)). Congress used "expansive

terms" in defining the four categories of inventions eligible for patent protection under § 101—processes, machines, manufactures, and compositions of matter. *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 308). In *Bilski*, this Court expressly noted that by using the comprehensive modifier "any," Congress "plainly contemplated that the patent laws would be given wide scope" and explained that "Congress took this permissive approach to patent eligibility to ensure that ingenuity should receive a liberal encouragement." *Id.* (internal quotation marks and citations omitted).

A. Technology Transfer Plays an Important Role in Translating the Results of Early-Stage Research Into Commercial Products.

Universities and research-based institutions[2] play a critical role in achieving the goals of the patent system and promoting innovation through the technology transfer process. Tech transfer is an important means by which scientific discoveries and inventions are transferred from universities to private-sector organizations for development, commercialization, and practical application. These are expensive, time-consuming, and risky investments that universities cannot make. The tech transfer process typically involves three stages: (1) discovery of a promising new technology; (2) obtaining of intellectual property protection of the

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[2] For simplicity, all institutions of this type will be referred to as "universities" throughout this *amicus* brief.

new technology through the filing of one or more patent applications; and (3) licensing of the applications and issued patents to the private sector to encourage and achieve further development, investment, and commercialization. For medical discoveries such as the patented treatment methods at issue in this appeal, tech transfer can be a key step in translating basic scientific research from the university researcher's laboratory "bench" to the patient's "bedside."

In their brief, Petitioners assert that "[p]atent protection assuredly is unnecessary to encourage or fund basic research of the sort reflected in the Prometheus patents, which is now routinely undertaken by scientists and researchers without regard to filing patents[,]" citing as support alleged "observations about the limited role of patents in encouraging medical research." *See* Brief for Petitioners ("Petitioners' Br.") at 21, 49-52. Petitioners' argument is a straw man, ignoring the ultimate goal of translating as much early-stage research as possible into publicly accessible diagnostic tools and therapeutic products that can prevent and cure disease.

Indeed, Petitioners' request for a sweeping new, narrow interpretation of § 101 would radically change the patent system and undermine efforts to encourage the development and commercialization of pioneering research conducted in our nation's universities. The development and commercialization path is long, arduous, and expensive. Patents are assets through which a university can pass on intellectual property rights to

small and frequently young companies focused on practical application of the technology. These companies, in turn, can pass them along to larger companies when greater capital is required to complete product development. The availability of intellectual property protection provides incentives to each entity along the development pathway to continue investing their capital as needed to bring a new invention to market. This process can be analogized to a relay race, with each participant passing along its patent rights like a baton. Not everyone finishes the race, but the incentive to persist is maintained by the promise of a limited period of exclusivity to market the ultimate product, the exclusivity defined in scope by the patents that surround it.

Because patents give inventions a tangible, legally transferrable form, their availability to cover the full range of innovative technologies is a fundamental premise of tech transfer. After filing patent applications on a promising new technology, a university actively seeks to license out to the private sector the applications and patents covering the technology. Most typically, the patent rights are licensed out exclusively, to a single licensee.[3] Unlike

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[3] In a federally-funded survey of licensing practices at nineteen of the thirty U.S. academic institutions that have received the largest number of DNA-related patents in the field of biotechnology, the data demonstrated that start-up companies obtained, in nearly all cases, exclusive licenses. *See* Lori Pressman, *et al.*, *The licensing of DNA patents by US academic institutions: an empirical survey*, 24(1) NATURE BIOTECHNOLOGY 31 (2006), at Figure 5. "Exclusive licensing is

universities, these companies have capital they can invest at risk in product development. With the promise of limited-term exclusionary rights afforded by the patent system, these companies have economic justification to undertake the time-consuming and expensive studies needed to test the observed results of a university's research, first in animals, then in human patients in clinical trials, as the FDA requires for regulatory approval. This framework has greatly benefited the public by allowing universities the means to achieve practical application of early-stage scientific research. It takes advantage of market efficiencies to leverage public and private resources, helps create jobs, improves public health outcomes, and stimulates the economy. At the same time, universities use the revenues realized through licensing to help advance scientific research and education, a further benefit to the public.

Petitioners' narrow theory—focused on the conduct of "basic" research by scientists in the laboratory—is short-sighted and far removed from the reality of medical innovation. Without the availability of patent protection to fuel the engine of tech transfer, medical research in academic laboratories would more often sit on the shelf, and the number and diversity of innovative discoveries entering the product development pipeline would decline.

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consistent with the need to lower the perceived risk of investing in unproven technology to attract private risk capital." *Id.* at 37.

In this case, the Prometheus method of treatment claims are directed to determining optimal dosages of thiopurine drugs for use in treating autoimmune disorders through measurement of certain metabolites or "biomarkers." All but one of the independent claims recite the steps of (1) "administering" a drug providing 6-thioguanine ("6-TG") (or a similar compound) to a subject, and (2) "determining" the level of 6-TG and/or 6-methyl-mercaptopurine ("6-MMP") in the subject's blood following administration of the drug.[4] The sole exception is one independent claim that omits the "administering" step. All independent claims conclude with one or more "wherein" clauses that specify certain circumstances when the levels of 6-TG or 6-MMP "indicate[] a need" to adjust the amount of drug administered to the subject. Such treatment methods, based upon analysis of the effects of specific drugs on individual patients, should clearly satisfy the broad patent-eligibility standard of § 101.

Research and development of this type, with the goal of optimizing medical treatments of individual patients, has spawned the new fields of personalized medicine and companion diagnostic testing.[5] The

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[4] 6-TG and 6-MMP are metabolites of 6-mercaptopurine ("6-MP"), which is a synthetic compound that can be used to treat autoimmune disorders.

[5] *See generally* Brief of *Amici Curiae* Roche Molecular Systems, Inc., Ventana Medical Systems, Inc., Hoffmann-La Roche Inc., and Abbott Laboratories, Inc. in Support of Neither Party, dated September 9, 2011.

societal value and cost-saving potential of advances in these fields was highlighted in a recent McKinsey publication, which reported that "[d]iagnostic tests are estimated to influence 60 to 70 percent of all treatment decisions, yet account for only 5 percent of hospital costs and 2 percent of Medicare expenditures." *See* February 2010 McKinsey Quarterly, *The microeconomics of personalized medicine*.[6] The availability of patent protection for inventions in these fields fosters innovation in biomedicine. Without it, many fewer inventions and discoveries would be transferred from "bench to bedside," and our nation's efforts to develop more effective and affordable healthcare would be hampered.

B. In Enacting the Bayh-Dole Act, Congress Recognized that the Patent System, with its Promise of Limited Exclusionary Rights, Is Critical to Spurring Commercialization of University Research for the Public Good.

In 1980, Congress responded to widespread concerns that the United States was losing its technological advantage and economic competitiveness in the global marketplace due to a perceived lack of innovation. It recognized that federal agencies that funded university research had imposed significant obstacles to commercialization of medical innovations and other new technologies

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[6] McKinsey's *The microeconomics of personalized medicine* is available at http://www.mckinseyquarterly.com/The_microeconomics_of_personalized_medicine_2527.

growing out of government-sponsored research. Importantly, the means Congress chose to overcome these obstacles was to amend the Patent Act, through enactment of the University and Small Business Patent Procedures Act of 1980, commonly known as the Bayh-Dole Act, 35 U.S.C. §§ 200-212.

The Bayh-Dole Act added an entirely new section to the patent statute, with the intent of "[using] the patent system to promote the utilization of inventions arising from federally supported research or development." Through Bayh-Dole, Congress expressly recognized that the promise of patent exclusivity was critical to incentivizing private sector investment in university technology. The importance and success of the Act has been borne out in the three decades since its passage.

One of the principal goals of the new tech transfer framework implemented by the Act was to solve the problem that universities were failing to interest private-sector companies in commercializing the universities' inventions because they could not offer licensees exclusive rights in the technology. This inability to obtain exclusive patent rights discouraged licensees from investing resources in university discoveries, as they could not expect to earn a reasonable return on such a long-term and risky investment or even recoup the development costs.

The Act's legislative history stresses the importance of using the patent system to allow exclusive licensing as a means to overcome the substantial costs and risks associated with

commercializing a new invention, particularly in the field of medicine. The Senate Report noted the estimate of many experts at the time "that the cost of taking a new invention from basic research through development and commercialization costs 10 times as much as did the basic research itself," and "a medical discovery faces lengthy, expensive regulatory procedures before any new medicine can be marketed." S. Rep. No. 96-480, at 19 (1979). Given these factors, the Report explains that "[w]hen [federal] agencies insist on retaining patent rights to medical discoveries and try to have them developed through nonexclusive licensing there are rarely any takers." *Id.* at 20.

To fix this problem, Congress provided a procedure by which universities and other non-profit research institutions are allowed to retain legal title to inventions made using federal research funds. The provisions of the Act encourage universities to file patents on the full range of their inventions and then collaborate with small businesses and other commercial enterprises to promote the development and utilization of the federally-funded discoveries, principally through licensing.[7] A paramount goal was to ensure that the universities' research would achieve practical application. *See* 35 U.S.C. § 203 (providing that funding agency retains "march-in" rights that can be exercised if contractor or licensee fails to take "effective steps to achieve practical

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[7] *See* 35 U.S.C. § 202, which sets forth the Act's provisions regarding disposition of patent rights.

application of the subject invention" within a reasonable time). The ability of universities to grant exclusive patent licenses is critical to this goal, because the chance of a limited period of exclusivity in the marketplace is what creates the economic incentive for companies to invest the enormous capital needed to obtain regulatory approval of new medical innovations. Disqualifying entire categories of innovative medical research from patent protection, as would be the result of Petitioners' proposed narrowing of patent eligibility, would defeat Congress's purpose in enacting Bayh-Dole.

The success of the Bayh-Dole Act in meeting its objectives is tangible and overwhelming. Since the Act took effect, more than 6,000 U.S. companies have been formed based on university discoveries; 4,350 university-licensed products are on the U.S. market; and 5,000 licenses between universities and industry are currently in effect. *See* AUTM's *2010 Better World Report: The Positive Impact of Academic Innovations on Quality of Life* ("*2010 Better World Report*"), at viii;[8] *see also The Bayh-Dole Act at 25*, at 22-25 (2006) ("*Bayh-Dole Act at 25*").[9] And of particular significance to the present appeal, more than 153 new medical products have been commercialized based on research funded by the

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[8] AUTM's *2010 Better World Report* is available at http://www.betterworldproject.net/AUTM2010BWR.pdf.

[9] The *Bayh-Dole Act at 25* white paper is available at http://www.bayhdolecentral.com/BayhDole25_WhitePaper.pdf.

U.S. government since enactment of the Act. *See 2010 Better World Report*, at viii.

Adopting Petitioners' narrow view of patent eligibility under § 101 on the theory that patents play an unnecessary role in fostering medical research would undermine Congress's reliance on the patent system through Bayh-Dole as the means to promote and assure the practical application of university-based research and innovation. Consistent with Congress's goals, this Court should reaffirm a standard of patent eligibility that broadly encompasses all fields of technology, including those not yet conceived or even imagined.

C. The Importance and Success of Technology Transfer in Driving Innovation is Shown By Licensing Activity Data and Real World Examples of Benefits Provided to the Public.

Recent data reported in the *AUTM U.S. Licensing Activity Survey Highlights: FY2010* ("*2010 Highlights*")[10] confirm the Bayh-Dole Act's positive impact on innovation and the continuing importance of tech transfer to universities, industry, and the U.S. public. The *2010 Highlights* includes tech

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[10] The *2010 Highlights* are available at http://www.autm.net/AM/Template.cfm?Section=FY_2010_Licensing_Survey&Template=/CM/ContentDisplay.cfm&ContentID=6874. These survey highlights were released in advance of the more comprehensive *AUTM U.S. Licensing Activity Survey: FY2010*, published in November 2011.

transfer data from 183 U.S. institutions, including 155 universities, 27 hospital and research institutes, and one third-party technology investment firm. According to the report, "[d]espite continuing difficult economic conditions, university and research institute licensing and startup activity remained very strong." *2010 Highlights* at 1. As support for this conclusion, the *2010 Highlights* cites the following data from 2010:

- 651 startup companies were formed, 5,362 licenses and options were executed, and 657 new commercial products were created.

- Total sponsored research expenditures were $59.1 billion, with $39.1 billion from the U.S. government and $4.3 billion from industry.

- 20,642 invention disclosures were received, 18,712 U.S. patent applications were submitted, and 4,469 U.S. patent were issued.

- Total licensing income was $2.4 billion.

The *AUTM U.S. Licensing Activity Survey Summary: FY2009* ("*2009 Summary*") includes similar data, and also highlights the significance of medical research in the tech transfer process. For example, the *2009 Summary* reports that nearly 50% of all invention disclosures that were able to be

categorized fell within the biomedical or life sciences areas. *See 2009 Summary* at 22. These included invention disclosures in the following fields: (1) Medical (e.g., therapeutic, pharmaceutical)—24.5%; (2) Biomedical Engineering—14.2%; and (3) Biological/Life Sciences (e.g., research tools)—10.4%. *Id.* at 23.

The successful operation of the tech transfer process can be further appreciated and understood through an actual example of the system at work.

At Beth Israel Deaconess Medical Center (BIDMC) in Boston, researchers discovered a new diagnostic test that warns mothers before preeclampsia strikes. Preeclampsia is a potentially dangerous complication of pregnancy that can afflict women as early as the twentieth week of gestation with little notice. According to the Preeclampsia Foundation, this disease affects 5 to 8 percent of all pregnant women—some 200,000 annually in the U.S. alone—and is responsible for more than 70,000 maternal and 500,000 infant deaths globally per year. The only cure for preeclampsia is forced labor or cesarean section to deliver the infant prematurely. According to Ananth Karumanchi, M.D., of BIDMC, "even though doctors know they will see many women with the disease, there has not previously been a way to tell which of them has preeclampsia until the onset of signs and symptoms." *See 2010 Better World Report* at 4.

Dr. Karumanchi and his team of researchers at BIDMC are developing the first diagnostic test for preeclampsia based on many years of careful

research. Dr. Karumanchi hypothesized that the placenta must be secreting toxic substances into the mother's blood, and indeed, one molecule in particular, sFLt-1, stood out as being very important. "We found that the sFlt-1 protein levels increased several weeks ahead of signs and symptoms. By finding that early warning marker, we now have a way to predict which women will suffer from the disease, and we can prepare early to address the problem," says Dr. Karumanchi. *Id.* at 5.

But the discovery did not arrive as a lightning strike: "There was no Eureka! moment. It took time for us to appreciate the discovery, and it took time for a number of colleagues across the field to confirm the findings," reports Dr. Karumanchi. *Id.* Based on this work, Dr. Karumanchi and his colleagues filed patent applications on their discoveries.

In 2005, BIDMC licensed the technology to Nephromics, and Nephromics in turn sublicensed the preeclampsia diagnostic test method to several leading diagnostic companies. In August 2011, Siemens Healthcare Diagnostics entered into a global licensing agreement with Nephromics to develop two assays to be used as an aid to the diagnosis of preeclampsia. "This story is a tremendous example of the marriage of great science, effective technology transfer and commercialization, leading to the development of a preeclampsia diagnostic. And we are lucky—it will

be accomplished in less than a decade," says Patrick Jeffries, president of Nephromics. *Id.* at 6.[11]

Recognizing the critical importance of innovation in medical technologies, the Food and Drug Administration recently issued a report entitled *Driving Biomedical Innovation: Initiatives to Improve Products for Patients* ("*Driving Biomedical Innovation*").[12] Focusing on the critical role of tech transfer to biomedical innovation, the October 2011 report notes that "[t]ranslating a new idea from a discovery into a medical product is a complex process involving an entire ecosystem consisting of academia, industry, small businesses, payors, physicians, government agencies, and patient and consumer groups." *Driving Biomedical Innovation* at 4. During a conference call discussing the report, FDA Commissioner Margaret Hamburg, M.D., explained that "it's very, very important that we have this kind of cross-fertilization, with industry and academia and government all working together to help ensure that we have the understanding and systems in place and the tools that we need to be

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[11] Numerous other examples of the tech transfer process at work can be found in AUTM's *2010 Better World Report*. *See supra* note 8.

[12] FDA's *Driving Biomedical Innovation* report is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274333.htm.

able to translate from scientific discoveries into real-world product."[13]

Tech transfer, in short, is a vital component of the innovation process. Imposing new limits on patent eligibility, as Petitioners propose, would set back the highly successful university-industry collaboration that has benefited the public over more than three decades since enactment of the Bayh-Dole Act.

D. Petitioners Ignore the Economic Realities That Play a Central Role in Bringing New Technologies to Market, as Their Own Actions Demonstrate.

Petitioners assert that Mayo Labs developed an improved product, and could have offered it at a lower price than the Prometheus product, but for the fact that Mayo Labs was blocked from launching it by Prometheus's patent lawsuit. *See* Petitioners' Br. at 8-11, 22. This assertion turns the patent bargain—early disclosure of inventions in exchange for a limited patent monopoly—on its head. As this Court has long recognized, the public benefits by having access to disclosures of inventions in order to build upon and improve them:

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[13] *See FDA Commish Hamburg Looks to Spur Med-Tech Innovation* (October 6, 2011), available at http://www.aimbe.org/2011/10/fda-commish-hamburg-looks-to-spur-med-tech-innovation/.

> The federal patent system . . . embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years. . . . In consideration of . . . disclosure and the consequent benefit to the community, the patent is granted.

Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 150-51 (1989) (internal quotation marks and citations omitted).

Mayo's "improvement" story is simply another example of the benefits of the patent bargain, not a reason to eliminate patent eligibility for innovations arising out of a vibrant and growing field of technology. The very reason Mayo Labs could develop a purportedly improved product and potentially offer it at a lower price point was that Mayo Labs was able to take advantage of the work disclosed by the inventors of Prometheus's patented methods, without incurring the initial investment Prometheus itself had made when it licensed the technology from the inventors. If patents are not available in fields like personalized medicine, inventors will be motivated to maintain critically significant data and discoveries as trade secrets in proprietary databases rather than disclose it to the public in patent applications, which are published eighteen months after they are filed in the U.S. Patent and Trademark Office ("USPTO").

In a similar vein, Petitioners complain that "no monopoly was necessary to incentivize the research that led to Prometheus's patents," and "Prometheus simply bought the right, after the fact, to patent [the inventors'] conclusions." Petitioners' Br. at 44. Once again, Petitioners fail to recognize how tech transfer operates to benefit the public. As discussed above, the tech transfer framework recognizes that research is a continuum, a partnership between research institutions and commercial enterprises, that serves the public. Tech transfer allows the private sector to acquire rights to research generated within universities and, through investment and marketing, turn it into commercial products that have practical application—the stated goal of the Bayh-Dole Act.

In this case, the inventors who worked at a Canadian teaching hospital entered into a licensing agreement with Prometheus. Prometheus then further developed and commercialized the inventors' method of treatment, making the test available to countless more patients than would otherwise have had access to it. Indeed, there was no commercial test of this type accessible to patients at all before Prometheus's product entered the market. This is exactly how tech transfer is meant to work.

Not surprisingly, it is Mayo Labs—a for-profit subsidiary of Mayo Clinic—that would have offered the "improved" test. This arrangement underscores that product development and commercialization is market driven, and that the economic profit motive is central to the ultimate goal of providing patients with access to innovative medical technologies.

Given this, Petitioners' complaints that the Prometheus patents operate as "bottlenecks on innovation competition" preventing others from "independently developing competing processes or products" ring hollow. *See* Petitioners' Br. at 45. Those complaints certainly do not support the restrictive standard for patent eligibility under § 101 that Mayo proposes.

The right to exclude others from practicing patented inventions for a limited term is the foundation of the patent system, as Petitioners well know.[14] Indeed, Mayo itself has obtained patents on methods and kits for determining the level of thiopurine methyltransferase activity in a biological sample, which presumably would have provided its "improved" test with patent protection from other competing laboratories interested in developing their own improvements to the test, and even today it has more such patents pending at the USPTO. *See* U.S. Patent Nos. 7,452,689 and 7,727,737; U.S. Patent Publication Nos. 2006/0263840 and 2009/0029399.

E. Petitioners' Policy Arguments Are Properly Addressed to Congress, Not This Court.

Petitioners' many policy arguments regarding the proper balance between incentivizing innovation

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[14] According to USPTO databases, more than 500 issued patents have been assigned to the "Mayo Foundation for Medical Education and Research" or other Mayo entities, and more than 300 published patent applications assigned to Mayo are currently under review at the USPTO.

and limiting competition (*see, e.g.*, Petitioners' Br. at 42-59) should be directed to Congress, not this Court. As the Court recently explained in *Microsoft Corp. v. i4i Limited Partnership*, 131 S. Ct. 2238 (2011), "Congress has amended the patent laws to account for concerns about 'bad' patents" in the past. *Id.* at 2252. And Congress will do so in the future, where warranted, as it did most recently in enacting the Leahy-Smith America Invents Act, signed into law in September 2011. Petitioners should address their request to narrow the scope of patent protection to Congress, as such issues "remain[] in its hands." *See id.*; *see also Bilski*, 130 S. Ct. at 3226 ("This Court has more than once cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed.") (internal quotation marks and citations omitted).

II. THE PROMETHEUS CLAIMS FALL WITHIN § 101'S BROAD PATENT-ELIGIBILITY STANDARD.

The Prometheus claims at issue in this appeal involve the steps of (1) "administering" a synthetic drug of a certain type and (2) "determining" the level of resulting metabolites in the subject's blood following administration of the synthetic drug. The claims conclude with one or more "wherein" clauses that specify circumstances when the metabolite

levels "indicate[] a need" to adjust the amount of synthetic drug administered to the subject.[15]

These claims fall squarely within the standard for patent eligibility adopted by this Court in *Diamond v. Diehr*, 450 U.S. 175 (1981), and reaffirmed in the Court's recent *Bilski* decision. In *Diehr*, this Court articulated a flexible test for determining patent-eligible subject matter designed to encompass new and evolving technologies and held that the process claims at issue—including several with "comparing" steps—fell within the scope of patent-eligible subject matter. While acknowledging that laws of nature, natural phenomena, and abstract ideas are excluded from the scope of § 101, the *Diehr* Court held that "an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." 450 U.S. at 187 (emphasis in original).

In an effort to provide guidance on the line between, for example, a natural phenomenon and a patent-eligible process that applies the natural phenomenon, this Court has repeated that an important clue to patentability is whether a process transforms or reduces an article to a different state or thing having concrete application. *See Bilski*, 130 S. Ct. at 3226-27. A "new and useful end" distinguishes an application of a law of nature, natural phenomenon, or abstract idea from those

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[15] As noted, one independent claim that omits the "administering" step.

concepts in isolation. *Diehr*, 450 U.S. at 188 n.11; *see also Bilski*, 130 S. Ct. at 3230 (summarizing *Diehr* holdings). The *Diehr* and *Bilski* Courts emphasized that this analysis must be applied to the claim *as a whole*, recognizing that inventions are, more often than not, new combinations of old elements and that it is therefore inappropriate to dissect a claim into separate elements to analyze its validity. *See Diehr*, 450 U.S. at 188; *Bilski*, 130 S. Ct. at 3230.

Petitioners ignore this Court's holdings in their attack on the Prometheus claims. First, they violate a fundamental tenet of the *Diehr* decision by characterizing the Prometheus invention as nothing more than a "correlation," arguing that the inventors of the Prometheus methods did not "'invent' [the] correlations between patient condition and metabolite levels, but merely recognized them as existing in the patient population that they studied." Petitioners' Br. at 5. This assertion is fundamentally flawed.

Read as a whole, each of the Prometheus claims meets the "transformation" test. Both the "administering" and "determining" steps of the claims involve transformations, supporting patent eligibility under § 101. Administering a man-made drug necessarily has the effect of transforming the human body, and determining the levels of metabolites in blood samples requires transformation of the samples though manipulation and measurement. *See Bilski*, 130 S. Ct. at 3226-27.

More broadly, the Prometheus patents are not claiming a natural phenomenon. The inventors recognized the usefulness of measuring certain specific metabolite levels in order to optimize administration of a particular category of synthetic drugs on a patient-by-patient basis to treat certain diseases. This "correlation" embodies the inventors' practical solution to the problem that individual patients metabolize these drugs differently, making effective dosing difficult and sometimes dangerous. Indeed, Mayo's own purported improvement on the Prometheus method underscores that the claimed method simply represents one group of inventors' practical solution to the problem based on their understanding of the drugs' effect on the human body; the claimed method is not an absolute truth, law of nature, or natural phenomenon.

Next, Petitioners argue that Prometheus's claims "preempt all practical uses of a natural phenomenon across a broad field" (Petitioners' Br. at 26), relying on *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972). This argument does not withstand analysis. *See, e.g.*, Brief of the United States as *Amicus Curiae* Supporting Neither Party ("U.S. Br."), dated September 9, 2011, 17-26.[16]

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[16] The United States points out that Petitioners' preemption argument fails for two reasons: "First, the [claimed] correlation is not a 'law of nature' or 'physical phenomenon' in the relevant sense because it exists only as the result of human intervention. Second, the claimed methods do not preempt all practical uses of the relationship between metabolite levels and

Petitioners broadly assert that patents claiming correlations between the administration of medication and a resulting biological effect can never be patent eligible under § 101. *See* Petitioners' Br. at 6, 47-48. Patents of this type, however, have long been recognized as claiming patent-eligible subject matter. *See* U.S. Br. at 9, 13-17. If Petitioners' position were true, innumerable patents directed to drug dose ranges and "effective amounts" of drugs would be invalid as claiming non-patentable subject matter under § 101, because dosages and effective amounts are fundamentally "correlations" between the administered drug and the resulting biological effect.

Adopting Petitioners' reasoning would adversely affect the entire biomedical field. Studies designed to identify appropriate amounts of drugs to be administered to a particular subpopulation of patients having a specific "biomarker" profile are costly and time-consuming, and patent protection is often needed to justify the investment in such studies. To hold that inventions directed to effective dosing based upon biomarker studies or other personalized treatment methods are ineligible for patent protection would greatly hinder the delivery of more efficient, focused, and cost-effective healthcare alternatives to patients in need.

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human health, at least if the correlation is described at an appropriately high level of generality." U.S. Br. at 18-19.

III. THE STRICT PATENTABILITY REQUIREMENTS OF §§ 102, 103, AND 112 SUFFICIENTLY PROTECT AGAINST THE ISSUANCE OF OVERBROAD PATENTS WITHOUT THE NEED FOR NARROWING THE STANDARD OF PATENT ELIGIBILITY.

As this Court recently reiterated, "[t]he § 101 patent-eligibility inquiry is only a threshold test." *Bilski*, 130 S. Ct. at 3225. Quoting § 101, the Court reinforced the fundamental concept that in order to qualify for patent protection "the claimed invention must also satisfy 'the conditions of patentability of this title.'" *Id.* These conditions of patentability are found in § 102 (novelty), § 103 (nonobviousness), and § 112 (disclosure requirements). The limitations found in §§ 102, 103, and 112 "serve a critical role in adjusting the tension, ever present in patent law, between stimulating innovation by protecting inventors and impeding progress by granting patents when not justified by the statutory design." *Id.* at 3229. As Justice Stevens wisely cautioned, concurring in *Bilski*:

> Given the many moving parts at work in the Patent Act, there is a risk of merely confirming our preconceived notions of what should be patentable or of seeing common attributes that track the familiar issues of novelty and obviousness that arise under other sections of the statute but are not relevant to § 101.

Id. at 3238 (internal quotation and citation omitted).

In the Patent Act, Congress recognized that the combination of a broad definition of patent *eligibility* with stringent conditions for *patentability* strikes a balance by encouraging innovation without unduly inhibiting competition.[17] *See id.* at 3225 ("Congress took this permissive approach to patentability to ensure that ingenuity should receive a liberal encouragement.") (internal quotation and citation omitted). This Court's precedents illustrate the stringent patentability requirements of §§ 102, 103, and 112 that serve as an effective gauntlet to evaluate claimed inventions that meet the broad patent-eligibility standard of § 101 but may not be deserving of patent protection.

Principles embodied in § 112, for example, bar sweeping, generalized claims attempting to reach beyond what an inventor has actually invented and disclosed to the public. In *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853), which is often cited as an early statutory subject matter case, the Court uses language that would, under current patent law, form the basis of a § 112 rejection for inadequate written description and/or enablement.

The Court allowed certain claims directed to Morse's telegraph invention, but rejected a claim directed to an abstraction of that invention—the use

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[17] A simple example illustrating this concept is state driver's licensing schemes, which have low eligibility criteria (often just minimum age and proof of residency) coupled with more stringent testing requirements that must be met prior to receiving a license.

of "electromagnetism, however developed for marking or printing intelligible characters, signs or letters, at any distances"—as attempting to claim any and all future methods of printing at a distance by means of the current, beyond what Morse had described or enabled. *Id.* at 119. In particular, the Court concluded that Morse invented the first seven of eight claims (those claims specifically pertaining to the telegraph and related applications of electromagnetism), but rejected the eighth because it claimed "an exclusive right to use a manner and process which [Morse] has not described and indeed had not invented, and therefore could not describe when he obtained his patent. The court is of the opinion that the claim is too broad, and not warranted by law." *Id.* at 114. In short, Morse was not entitled to such a broad claim because "he claims what he has not described in the manner required by law." *Id.* at 120.

As the Court of Appeals for the Federal Circuit recently explained in an unrelated case, "an invention which is not so manifestly abstract as to over-ride the statutory language of section 101 may nonetheless lack sufficient concrete disclosure to warrant a patent. In section 112, the Patent Act provides powerful tools to weed out claims that may present a vague or indefinite disclosure of the invention." *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 869 (Fed. Cir. 2010).

Likewise, §§ 102 and 103 establish strict patentability requirements of novelty and non-obviousness. These are high hurdles. Where there is concern that an applicant improperly seeks to

capture inventions and knowledge already in the public domain, § 102 will block the issuance of patents because they lack the requisite novelty. Thus, for example, under § 102, an applicant is not entitled to obtain a patent for merely recognizing particular properties inherent in the prior art, even if such properties had not previously been recognized by persons skilled in the art. *See, e.g., In re Cruciferous Sprout Litig.*, 301 F. 3d 1343, 1349-51 (Fed. Cir. 2002).

Section 103 casts an even broader net, barring the issuance of patents claiming obvious variants of known inventions or combinations thereof, because "a patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what already is known into the field of its monopoly and diminishes the resources available to skillful men." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415-16 (2007) (alteration in original; internal quotation marks and citations omitted); *see also id.* at 416 ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

This Court's precedent has recognized the balance achieved by counter-balancing the broad eligibility standard of § 101 with the exacting patentability requirements imposed by §§ 102, 103, and 112. In *Diehr*, the Court explained that the question of whether patent claims fall within the § 101 categories of possibly patentable subject matter is very different from the question of whether the patentability conditions of §§ 102, 103, and 112

are met. 450 U.S. at 191. The *Diehr* Court concluded that, although a claimed process may not be "deserving of patent protection because it fails to satisfy the statutory conditions of novelty under § 102 or nonobviousness under § 103 [,a] rejection on either of these grounds does not affect the determination that [the claimed process] recited subject matter which was eligible for patent protection under § 101."[18] *Id.*

In their brief, Petitioners repeatedly argue that Prometheus's patented methods were well known and had been performed by doctors for many years. *See, e.g.,* Petitioners' Br. at 21, 24, 25, 34-37. However, questions as to whether claimed inventions were "well known" and in the public domain are controlled by the novelty requirement of § 102, not by the eligibility requirement of § 101, the sole issue on appeal here. The Court's consideration of § 101 eligibility here should disregard issues properly addressed under § 102 (and §§ 103 and 112).

For these reasons, and the reasons set forth in Section II above, the Prometheus claims are "at the very least not barred at the threshold by § 101." *See Diehr*, 450 U.S. at 188. Whether the claims meet the

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[18] Although not expressly stated by the *Diehr* Court, this analysis would equally apply to the disclosure requirements of § 112, *i.e.*, failure to satisfy § 112 would not affect the determination that a claimed invention "recited subject matter which was eligible for patent protection under § 101." *See id.*

strict conditions of patentability of §§ 102, 103, and 112 are separate questions reserved for another day.

CONCLUSION

For the foregoing reasons, AUTM urges this Court to affirm the judgment of the court of appeals and reject Petitioners' attempt improperly to narrow the scope of patent eligibility under § 101.

Respectfully submitted,

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November 7, 2011

AMICUS CURIAE BRIEF

No. 10-1150

IN THE
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF THE BIOTECHNOLOGY INDUSTRY ORGANIZATION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF THE *AMICUS CURIAE*

The Biotechnology Industry Organization (BIO) is a trade association representing over 1,100 companies, academic institutions, and biotechnology centers. BIO members are involved in researching and developing healthcare, agricultural, environmental, and industrial products.[1] The biotechnology industry currently has more than 370 products in clinical trials for treating more than 200 diseases. The vast majority of BIO members are small companies that have not yet brought a product to market or attained profitability.

The biotechnology industry is uniquely dependent on predictable and effective patent protection for the development of new technologies. This is because investors such as venture capitalists in large measure base their decisions whether to invest in early-stage companies—thereby funding the research and development that eventually will bring new products to market—on the availability of patent protection for an asset that can be commercialized. Innovation in our industry thus depends upon predictability and transparency in the procurement and enforcement of patent rights. BIO therefore promotes the adoption and application of standards for patent eligibility that will ensure appropriate and consistent protection for inventions in the biotechnology sector.

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[1] Pursuant to Supreme Court Rule 37.6, *amicus curiae* states that no counsel for a party authored this brief in whole or in part, and no entity or person other than *amicus curiae*, its members, and its counsel, made any monetary contribution toward the preparation or submission of this brief. Mayo Clinic is a member of BIO but did not participate in the consideration or preparation of this brief. Letters from the parties consenting to the filing of this brief are on file with the Clerk.

SUMMARY OF THE ARGUMENT

To exclude categories of inventions from patent eligibility under 35 U.S.C. § 101 has the potential to do tremendous damage to innovation affecting entire sectors of the economy. This is because, unlike a measured and focused inquiry into the merits of a particular invention—such as whether it is sufficiently new and useful—a rule of patent-eligibility concerning classes of inventions simply eliminates the patent incentive for that class of technology. This Court previously has recognized the danger inherent in "adopting categorical rules that might have wide-ranging and unforeseen impacts." *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3229 (2010).

That danger is present in this case. Announcing a broad rule of ineligibility concerning diagnostic and therapeutic methods that exploit knowledge gained from the study of biological systems would threaten harm to the biotechnology industry, and devastation to the nascent field of "personalized medicine," which promises substantial benefits to patients through its capacity to match focused and appropriate treatments and improved diagnostic methods.

In a time when health-care costs continue to increase, personalized medicine promises to yield substantial savings. *See* BIO, *Guide to Biotechnology 2008*, at 35 (2008), *available at* http://www.bio.org/sites/default/files/BiotechGuide2008.pdf ("*Guide to Biotechnology*"). Personalized medicine, also called targeted therapy, entails the use of individual genetic information to select medicines and treatments that precisely match the needs of a patient. *Id.* Personalized medicine therefore saves health-care dollars by targeting treatments to those patients most likely to respond to them. And medicines that have been abandoned because they may have shown low efficacy

rates on the population as a whole may be put to effective use in treating a particular subpopulation of patients in which those drugs can be shown to be effective. But this important and growing field is threatened by the arguments advocated by Petitioners, and BIO therefore urges that the Court take a cautious approach in applying § 101 to the field.

Like inventions in many other fields of technology, inventions in the field of personalized medicine often exploit known elements and discoveries. They do so, however, in the service of new and useful ways of diagnosing and treating patients. The inventive spark—a spark that is lit by extensive funding and research—occurs when a scientist connects the dots between these known and unknown elements, such as by using biomarkers to devise a new way of selecting patients, identifying symptoms that can be associated with a disease or using a drug to treat those patients, or selecting a drug that does not trigger adverse reactions in the patient. The result of these insights—a novel and useful method or treatment—is and should remain patent-eligible.

To be sure, every invention must satisfy each of the requirements of patentability to warrant the grant of a patent. If the invention is anticipated by some prior art, see 35 U.S.C. § 102, or obvious in view of that prior art, *id.* § 103, it should not be awarded a patent. Similarly, if the breadth of the rights awarded by a patent claim are not in proportion to the disclosure made by the inventor in the patent, that may warrant holding the patent claim invalid. *Id.* § 112. Indeed, much of the thrust of Petitioners' complaint is that the patents at issue in this case encompass elements that were commonly known to researchers or clinicians. But if true, that fact may render the patent claims invalid for reasons entirely unrelated

to § 101. The question whether these claims meet the requirements of §§ 102, 103, and 112, however, is not presently before the Court, and the Court should not use patent-eligibility as a surrogate for addressing questions properly addressed under those separate statutory provisions.

Rather than adopt the broad holding under § 101 that Petitioners advocate, this Court should reiterate two fundamental principles that it has applied for decades, and under which the claims at issue in this case define inventions that are patent-eligible, regardless whether they ultimately are determined to be valid.

First, the Court should emphasize that in reviewing a claim under § 101, courts must consider the claim *as a whole*. Courts should not, as Petitioners request, dissect the claims into discrete elements and then ignore any individual claim element deemed to be known or "insignificant." The settled rule against doing so is particularly important to personalized medicine for the reasons just set forth—a personalized medicine process may and often will draw upon known steps or components to yield an overall process that is important, valuable, and deserving of patent protection. The claim-dissection approach advocated by Petitioners would plunge the patent system into a standardless, "eye of the beholder" system for measuring an invention's merit. This would fundamentally erode the patent incentive for all innovators by making it impossible for inventors to know in advance whether they can secure patent rights in their inventions. Moreover, this approach would run counter to decades of guidance from this Court, which long ago recognized that claim-dissection distorts the invention during its evaluation for patent entitlement.

Second, the Court should reaffirm that, although a law of nature, natural phenomenon, or abstract idea is not itself patentable subject matter, a particular *application* of that law of nature, natural phenomenon, or idea is. It is well-established and has been long understood that an invention is not excluded from patent-eligibility under § 101 merely because it harnesses natural or biological processes. But Petitioners seem to advance a rule whereby not only natural phenomena and laws of nature would be excluded from patent-eligibility, but also some ill-defined subset of applications of those laws of nature or natural phenonema. The Court should squarely reject this rule, and reaffirm its prior precedents. Holding otherwise would interpose insurmountable obstacles to securing patent protection in the field of life sciences, as virtually all inventions in this field draw upon biological systems, or seek to exploit or affect their function.

The progress of the biotechnology industry over the 30 years of its existence has demonstrated that patent protection is an essential driver of innovation. The role that patents have played for this industry, and which they must play to encourage innovation in the field of personalized medicine, is exactly the role that Patent Clause envisions. See U.S. Const. art. I, § 8, cl. 8; *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 146 (1989). Using § 101 to broadly exclude entire categories of new and useful inventions from patent eligibility would be antithetical to this basic purpose. BIO urges the Court to deploy § 101 cautiously, because the danger of unforeseen consequences is great.

ARGUMENT

THE COURT SHOULD HEED THE FUNDAMENTAL PRINCIPLES IT HAS PREVIOUSLY APPLIED IN DETERMINING PATENT ELIGIBILITY.

A hallmark of our patent law is that it protects, and thereby fosters, emerging technologies whose commercial potential may not yet be fully understood or appreciated. This feature of the patent system is critical to economic growth,[2] which is precisely why the provisions of the Patent Act concerning the threshold question of patent eligibility were framed in such broad terms: "The subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts' with all that means for the social and economic benefits envisioned by Jefferson." *Diamond* v. *Chakrabarty*, 447 U.S. 303, 315 (1980).[3] A contrary rule—"that unanticipated inventions are without protection"—"would conflict with the core concept of

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[2] *See* H.R. Rep. No. 112-98, pt. 1, at 73 (2011) (purpose of the America Invents Act, the recent patent-reform bill, is to "spur innovation as a means to create American jobs and raise standards of living"); Fed. Trade Comm'n, *To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy* 1 (Oct. 2003), *available at* http://www.ftc.gov/os/2003/10/innovationrpt.pdf ("Innovation benefits consumers through the development of new and improved goods, services, and processes. An economy's capacity for invention and innovation helps drive its economic growth and the degree to which standards of living increase.").

[3] *See also Chakrabarty*, 447 U.S. at 308 ("In choosing such expansive terms" in the definition of patentable subject matter "modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope.").

the patent law that anticipation undermines patentability." *Id.* at 316.

For this basic reason, the Court repeatedly has recognized the need to exercise caution before excluding some domain of inventive activity from the protection of the patent laws. Unlike defects with particular patents, which may be dealt with on a case-by-case basis in a court or the Patent & Trademark Office, sweeping determinations of patent-ineligibility amount to policy determinations that generally are not well suited to judicial resolution on a categorical basis:

> Should certain classes of invention be treated in one way and other classes differently? These are not legal questions, which courts are competent to answer. They are practical questions, and the decision as to what will accomplish the greatest good for the inventor, the government, and the public rests with the Congress. We should not read into the patent laws limitations and conditions which the Legislature has not expressed.

United States v. *Dubilier Condenser Corp.*, 289 U.S. 178, 198-99 (1933); accord *Diamond* v. *Diehr*, 450 U.S. 175, 182 (1981) (the Court has "more than once cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed" (internal quotation marks omitted)).

Against this backdrop, the Court has recognized only three exceptions to patent-eligibility—namely, claims that define natural phenomena, laws of nature, and abstract ideas. *Chakrabarty*, 447 U.S. at 309. But, the existence of these "well-established exceptions" does not "give[] the Judiciary *carte blanche* to impose other limitations that are incon-

sistent with the text and the statute's purpose and design." *Bilski*, 130 S. Ct. at 3226. This is because "[t]he § 101 patent-eligibility inquiry is only a threshold test." *Id.* at 3225. It is, as the PTO has explained, a "coarse filter." U.S. Patent & Trademark Office, *Interim Guidance for Determining Subject Matter Eligibility for Process Claims in View of* Bilski v. Kappos, 75 Fed. Reg. 43922, 43926 (July 27, 2010).[4]

The capacity of the patent system to foster development of new technology is proven by the history of the biotechnology industry. The inventions that have led to the growth and success of biotechnology, both as a scientific and engineering discipline and as an industry, could not have been imagined when the Patent Act was rewritten in 1952. An inclusive standard for patent eligibility has proven essential to the successful development and commercialization of over 200 biotechnology therapies and vaccines, hundreds of diagnostic tests, and pest- and herbicide-

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[4] The patent claims at issue in this case plainly satisfy this inquiry. They do not disclose a natural phenomenon, as there is nothing "natural" about the processes claimed here. A man-made drug that does not exist in nature is administered to a patient through artificial means. Pharmacologically potent active metabolites that do not occur under natural conditions are then analyzed through sophisticated laboratory processes. The patents also do not claim a law of nature, like the law of gravity or $E=mc^2$. Whereas those laws operate universally and independently of human endeavor, the claimed invention is a human-devised way of interfering with the natural course of a human disease that, if untreated, would get only progressively worse. And, the patents do not claim an abstract idea. The claims recite concrete steps—administering a drug and determining the levels of particular metabolites in plasma—taken to reach a specific result. Whether or not the claims are anticipated or obvious in light of prior art, they define a patent-*eligible* process.

resistant crops. See *Guide to Biotechnology* at 2. This is particularly true because "[b]iotechnology is one of the most research-intensive industries in the world." *Id.* U.S. publicly traded biotech companies spent $22.8 billion on research and development in 2010. Ernst & Young, *Beyond Borders: Global Biotechnology Report 2011*, at 37 (2011), *available at* http://tinyurl.com/5u9o5bd.

But, just as the patent system may encourage innovation, it carries the converse danger that court-adopted rules trimming away patent eligibility may hinder such technological advance. This concern is particularly great where personalized medicine is concerned. BIO therefore urges the Court to reaffirm two basic principles, both of which are critically important to the biotechnology industry generally, and personalized medicine specifically, and which BIO discusses in greater detail below. Specifically, the Court should reaffirm that "claim dissection" is not an appropriate way to evaluate patent claims for eligibility. *Infra* Section A. A rule which calls for courts or the PTO to pick apart an invention in the way Petitioners advocate, disregarding the old and focusing only on the new or "significant" elements, will inherently diminish and distort the importance of every invention—and especially inventions that build upon prior knowledge or discoveries but which do so through important, patentable leaps of inventive genius.

In addition, the Court should reaffirm that although natural phenomena and laws of nature are not patentable, *applications* of them certainly are. *Infra* Section B. Certain of Petitioners' arguments seem to call into question this basic rule, and any decision of the Court accepting Petitioners' invitation

will have highly detrimental consequences in the biotechnology industry.

A. Patent-Eligibility Must Be Determined By Considering The Claim As A Whole.

1. Petitioners suggest repeatedly that in evaluating the patent-eligibility of the claims, the Court may disregard aspects of the invention that are non-novel. In effect, Petitioners urge whittling away the invention, leaving what it claims is a non-patent-*eligible* core. *E.g.*, Pet. Br. 24 ("The drugs involved and the method of blood testing for metabolites are well known and have been used by physicians and researchers for decades."); *id.* at 35 (asking the Court to ignore steps in the claimed process that are "preparatory" or "'data-gathering'" steps, or "ordinary means of observing the natural correlation").

The Court should reject this argument, which has no place in analyzing patent eligibility. The Court has previously and properly criticized the use of a "claim dissection" approach when reviewing a claim for patentability. Instead, it has explained,

> claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made. The "novelty" of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter.

Diehr, 450 U.S. at 188-89; *accord Bilski*, 130 S. Ct. at 3230 (describing and relying upon *Diehr*); *Application of Chatfield*, 545 F.2d 152, 158 (C.C.P.A. 1976) ("We have thus specifically rejected the broad notion that if a portion of a claim be non-statutory the whole claim is ipso facto non-statutory. The requirement is that the invention set forth in a claim be construed as a whole").

The dangers inherent in a contrary approach are manifest. An analysis of patent-eligibility that starts by dissecting a claim into pieces invites litigants to focus on process steps that appear to be algorithms, decision-points, or that otherwise make use of data—i.e., "solution" steps that appear central to the claimed process. But once the analysis is thus focused, preceding and subsequent claim steps naturally will appear to be no more than pre- and post-solution activity, and proper focus on the claim as a whole will be lost, and with it a proper understanding of what the inventor actually invented. This is why, even in the context of evaluating whether an invention is obvious—a fact-intensive inquiry that is necessarily more searching than the "coarse filter" of patentability—the Court has recognized the danger of picking apart inventions in the fashion Petitioners advocate:

> [A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the

> elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

KSR Int'l Co. v. *Teleflex Inc.*, 550 U.S. 398, 418-19 (2007).

2. Applying the basic rule against claim dissection is particularly important in the domain of personalized medicine, where, in the language of *Diehr*, "a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made." 450 U.S. at 188. Taken to its logical conclusion, claim-dissection could call into question many process claims that use data generated from a biological system. Such claims will frequently require the gathering of information and so, as we discuss next, individual steps in a treatment protocol or diagnostic process may be familiar, using known testing techniques or isolating known compounds. But although certain of this knowledge may be familiar, the technique for applying the knowledge through treatment or diagnosis will not be. The results are new and useful diagnostic or therapeutic procedures, which the patent laws should properly recognize as patentable subject matter.

An example demonstrates the point. The anticancer drug irinotecan first received conditional marketing authorization by the FDA in 1996, and full approval as second-line therapy for patients with metastatic colorectal cancer in September 1998.[5] Irinotecan,

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[5] *See* Pfizer, *Background Document on the UGT1A1 Polymorphisms and Irinotecan Toxicity* 3 (2004), *available at* http://

however, was found to cause severe adverse effects in certain patients. Those effects were unpredictable, and the inability to predict which patients would suffer these potentially fatal toxicities became an important factor for physicians who considered adopting this important new drug in clinical practice.

Subsequent studies suggested that interpatient variability in the toxicity of irinotecan might be related to genetic factors. Scientists homed in on a particular mutation of the UGT1A1 gene that had long been known to be associated with Gilbert's syndrome, an inherited metabolic disease unrelated to colon cancer.[6] It was found that the presence of this particular mutation explains not only the metabolic symptoms of Gilbert's syndrome, but also predicts the risk of severe irinotecan side effects in the completely different context of colon cancer therapy.[7] This finding triggered repeated revisions of the drug's label to warn that reduced dosing of irinotecan is recommended in patients who carry certain forms of the UGT1A1 gene.[8] The use of

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www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079B1_07_Pfizer-UGT1A1.pdf.

[6] *See* Piter J. Bosma et al., *The Genetic Basis of the Reduced Expression of Bilirubin UDP-Glucuronosyltransferase 1 in Gilbert's Syndrome*, 333 New England J. Med. 1171 (1995).

[7] L. Iyer et al., *UGT1A1*28 Polymorphism as a Determinant of Irinotecan Disposition and Toxicity*, 2 Pharmacogenomics J. 43 (2002); Federico Innocenti et al., *Genetic Variants in the UDP-Glucuronosyltransferase 1A1 Gene Predict the Risk of Severe Neutropenia of Irinotecan*, 22 J. Clinical Oncology 1382 (2004).

[8] Yael Waknine, *FDA Safety Labeling Changes: Camptosar, Keppra, Prempro/Premphase*, Medscape News (Sept. 21, 2005), http://www.medscape.com/viewarticle/513175; *Camptosar (iriotecan HCL) injection*, FDA Safety (May 2010), http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm215480.htm

UGT1A1 testing for predicting irinotecan toxicity was patented by researchers at the University of Chicago[9] and exclusively licensed to Mayo Clinic, which sublicensed the rights to clinical laboratories and uses the revenues to support research and education.[10]

Today, UGT1A1 testing is an important part of personalized colon cancer therapy with irinotecan. And, importantly for present purposes, the Gilbert's Syndrome mutation, irinotecan, and its toxicity were all individually known at the time costly clinical research established the connection between the three. The invention was in connecting the dots, and developing a patentable process for commercializing that invention. Doing so created a substantial and novel benefit to numerous colon cancer patients.

3. The claim-dissection approach urged by Petitioners is particularly ill-advised because the patent law already contains more focused mechanisms for evaluating the patentability of particular claims. If a piece of prior art describes each limitation of the asserted claim, then the claim may be held invalid as anticipated. 35 U.S.C. § 102. If an asserted claim is obvious—that is, if "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious"—then it may be invalidated on

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[9] U.S. Patent No. 6,395,481 (claim 62).

[10] Press Release, Univ. of Chi. Med. Ctr., University of Chicago researchers license pharmacogenomics test for patients with colorectal cancer to Mayo Clinic (Dec. 21, 2005), http://www.uchospitals.edu/news/2005/20051221-ugt1a1.html; Press Release, Univ. of Chi., Gene screen patent leads to 'Deal of Distinction' for University of Chicago (Oct. 29, 2007), http://www-news.uchicago.edu/releases/07/071029.licensing.shtml.

that basis. *Id.* § 103. And if a claim confers an imprecise or excessive scope of rights relative to what the inventor has taught and disclosed in the patent, the claims may be refused or held invalid. See *BJ Servs. Co.* v. *Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1371 (Fed. Cir. 2003) (claim invalid if description does not "enable" one of ordinary skill in the art to practice the full scope of the invention); *Source Search Techs., LLC* v. *LendingTree, LLC*, 588 F.3d 1063, 1076 (Fed. Cir. 2009) (claim invalid as indefinite if it cannot be construed); *Ariad Pharm., Inc.* v. *Eli Lilly & Co.*, 598 F.3d 1336, 1344 (Fed. Cir. 2010) (en banc) (claim invalid if patent does not contain adequate "written description" of what is claimed).

It is telling, indeed, that Petitioners depend repeatedly on the considerations relevant to these other criteria of patentability to advance their attack on the claims under § 101. Petitioners insinuate repeatedly that aspects of Respondent's asserted claims are known in the art. See, *e.g.*, Question Presented ("well-known methods"); Pet. Br. 3 ("[a]ll doctors know"), 4 ("Thiopurine drugs have been administered for decades, and ... the appropriate levels of thiopurine metabolites in patients have been measured, studied, and discussed for many years."), 5 ("the inventors freely disclosed"), 21 ("discovered over thirty years ago"), 21 ("For decades"), 22 ("have long done"), 24 ("The drugs involved and the method of blood testing for metabolites are well known and have been used by physicians and researchers for decades."), 25 ("doctors and researchers ... considered metabolite levels on their own years before these patent claims were filed"), 36 ("Well-known, non-inventive steps cannot turn a natural phenomenon into patentable subject matter."), 39 ("as physicians long have done"), 44 ("well known to physicians for many years").

If Petitioners wish to argue that the asserted claims are anticipated by prior art, that they are so well-known that the claims are obvious, or that the claims omit limitations that make them correspond to the disclosure provided by the patentee, then Petitioners may raise those objections in due course. *Cf.* U.S. Br. 26-33.[11] But it is those requirements of patentability that provide the proper conduit for Petitioners' objections, not least of all because those doctrines have a significant advantage over consideration of patent-eligibility: They cut narrowly, rather than sweep broadly.

Anticipation, for instance, requires a comparison between the asserted claim and the purportedly prior-art reference to see whether the prior art describes "each and every claim limitation." *Iovate Health Scis., Inc.* v. *Bio-Engineered Supplements & Nutrition, Inc.*, 586 F.3d 1376, 1380 (Fed. Cir. 2009). It is a factual determination, and thereby is litigated as such. *Finisar Corp.* v. *DirecTV Grp., Inc.*, 523 F.3d 1323, 1334 (Fed. Cir. 2008). Obviousness, while considering the invention "as a whole," 35 U.S.C. § 103, of necessity focuses on the elements of the claim to determine whether, both individually and in combination, they would have been considered obvious from the prior art to a person of ordinary skill. *E.g.*, *Unigene Labs., Inc.* v. *Apotex, Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011); *Princeton Biochemicals, Inc.* v. *Beckman Coulter, Inc.*, 411 F.3d

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[11] It would be particularly inadvisable to announce broad rules concerning patent-eligibility, with the concomitant adverse consequences, merely because of the fortuity that this case arises in an interlocutory posture. The district court held the claims patent-ineligible under § 101 without addressing anticipation or obviousness, and the Federal Circuit reversed the § 101 determination. *See* Pet. App. 7a-8a, 23a, 83a.

1332, 1337-38 (Fed. Cir. 2005). The numerous inquiries underlying an obviousness determination are questions of fact. *Graham* v. *John Deere Co. of Kansas City*, 383 U.S. 1, 17 (1966). The inquiries mandated by § 112 similarly are focused on the claims, demanding a proper correspondence between what has been taught and described by the inventor and what the claims encompass. *E.g.*, *AK Steel Corp.* v. *Sollac*, 344 F.3d 1234, 1242-44 (Fed. Cir. 2003); *Exxon Research & Eng'g Co.* v. *United States*, 265 F.3d 1371, 1380-81 (Fed. Cir. 2001); *Ariad*, 598 F.3d at 1347. In short, the analysis compelled by these conditions of patentability is fact- and patent-specific, with the consequence that finding one particular invention undeserving of patent protection does not create risks for an industry as a whole. By contrast, an interpretation of § 101 that excludes a class of invention from the realm of patent law altogether necessarily will have widespread effects.

4. While asking the Court to ignore certain elements of the claims, Petitioners also attack the claims for "not recit[ing] the administration of any amount of any drug to be given to any patient." Pet. Br. 24 n.5; see also *id.* at 22 (claims "do not offer any specific change in therapy"). But inventors in the field of personalized medicine must be able to protect their inventions in a commercially effective manner, and the example of irinotecan toxicity proves the impracticability of imposing such a requirement. Discovering the correlation between the UGT1A1 gene and irinotecan toxicity required substantial investment and produced substantial benefits. As a practical matter, it permits use of the correlation to increase treatment effectiveness, including by determining the presence or absence of the relevant mutation, and deciding to act on that diagnostic inform-

ation. But requiring an administration step whereby the dose is adjusted—much less as a condition of patentability—would sap the invention's commercial value.

If, for instance, only one in ten patients has the mutation, then the drug dose would be adjusted in only one out of ten applications of the process, and the process as patented would be practiced in only 10% of applications. The value of the invention, however, lies in the determination of whether an adjustment is needed in advance of administration of the agent. A contrary rule would enable a competing laboratory to extract 90% of the test's real commercial value without facing infringement liability.[12] The patentee, on the other hand, who through his efforts created a market for a laboratory service where none had existed before, would be able to realize no more than 10% of the invention's commercial value.[13]

If biotechnology inventions are deemed patent-eligible only to the extent that they include limitations that render their invention nearly commercially irrelevant, then patent protection will

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[12] Indeed, in the irinotecan example, only about 10% of patients carry two copies of the mutation that predisposes them to irinotecan toxicity, placing them at a high risk of side effects. Accordingly, the University of Chicago's patent on a "method for optimizing [irinotecan] dosages" requires only a determination of certain polymorphisms in the UGT1 gene; like Prometheus's claim, the claim does not require the actual administration of an optimized dose. *See* U.S. Patent No. 6,395,481 (claim 62).

[13] Nor would the patentee be able to capture the remaining commercial value through a claim that comprises the steps of assaying for the biomarker and "not adjusting the dose if the biomarker is not present." Negative claim elements are normally improper and not allowable in the PTO, because they add no limitation to the claim.

be worth very little. The law does not support such a result. *See* Resp. Br. 34-36 (explaining that "Section 101 does not categorically exclude processes that end by providing useful information" rather than a physical step) (capitalization omitted). The plain result of any such rule would be less research, less discovery, and less "promot[ion of] the Progress of Science." U.S. Const. art. I, § 8, cl. 8. Biotechnology inventions are driven by expensive clinical trials, complicated laboratory tests, and computerized analysis of large amounts of data under complex algorithms. As other amici have explained, such investments can be significant, and often would not occur without the patent incentive. Br. for Amici Curiae Roche Molecular Systems, Inc., et al. ("Roche/Abbott Br.") 13-19.

The danger of these profoundly negative consequences for public health is the reason Petitioners feel compelled to argue that government and academia will step in. Pet. Br. 51. This is cold comfort. In a recessionary era of steep budget cutbacks, speculation about government support is worth very little. And, more importantly, this is not the system the Framers envisioned. Petitioners point to no support for the notion that patent protection should be obviated because of the potential for alternate funding sources for research. This is because the basic premise of the patent system, from the time of Thomas Jefferson forward, is that the best way to "promote the Progress of Science" is by "securing for limited Times to ... Inventors the exclusive Right to their ... Discoveries." U.S. Const. art. I, § 8, cl. 8; see *Graham*, 383 U.S. at 9 n.2 ("'Society may give an exclusive right to the profits arising from [inventions], as an encouragement to men to pursue ideas which may produce utility....'") (quoting Letter from Thomas Jefferson to Isaac McPherson (Aug. 13, 1813) *in* 6

Writings of Thomas Jefferson 181 (Henry Augustine Washington ed., 1853)).

Moreover, academic and government-focused research commonly focuses on early-stage research, while research funding from the private sector often emphasizes paths of research that will yield new products and services. Indeed, the federal government's inability to commercialize inventions was a major purpose of the University and Small Business Patent Procedures Act of 1980, 35 U.S.C. §§ 200 *et seq.*: the sponsors of that legislation recognized that "[i]f the results of federally sponsored research were to be rescued from oblivion and successfully developed into commercial products, they would have to be patented and offered up for private appropriation." Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 Va. L. Rev. 1663, 1664 (1996). Here, eliminating the patent incentive will be particularly harmful to the focused research and development efforts that are needed to bring innovative new products and services to market to benefit patients.

If this Court adopts the broad theory urged by Petitioners, the impact on investment in personalized medicine products is likely to be profound.

B. While Natural Phenomena Are Not Eligible For Patenting, New And Useful Applications Of Them Always Have Been And Should Remain So.

The law has long recognized "the true distinction between a mere principle, as the subject of a patent, and a process by which a principle is applied to effect a useful result." *Tilghman* v. *Proctor*, 102 U.S. 707, 724 (1880); see also, *e.g.*, *Mackay Radio & Tel. Co.* v.

Radio Corp. of Am., 306 U.S. 86, 94 (1939) ("While a scientific truth, or the mathematical expression of it, is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be."). Thus, even if a natural phenomenon or principle is itself ineligible for patenting, a method, article, composition or machine that makes use of such a phenomenon or principle to achieve a concrete, useful end remains patentable. See, *e.g.*, *Diehr*, 450 U.S. at 187 (process that "admittedly employs a well-known mathematical equation" to cure synthetic rubber is patentable subject matter).

The analysis that Petitioners ask the Court to adopt would call this fundamental principle into question. The premise of Petitioners' argument is that "Prometheus's patents recite a natural phenomenon—the biological correlation between metabolite levels and health." Pet. Br. 18.[14] On Petitioners' view, it seems, the Court should ignore the transformative steps in the asserted patent and examine only whether the correlation itself can be patented. To accept Petitioners' premise would seriously undermine the longstanding tenet that an *application* of a natural phenomenon is patent-eligible. Any decision that calls into question this basic principle, either expressly or by implication, will have drastic consequences

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[14] *See also* Pet. Br. Question Presented (patent grants a "sweeping monopoly on a biological correlation between drug administration and natural changes in blood chemistry"); *id.* at 33 ("Prometheus's patents recite a natural phenomenon—the biological correlation between metabolite levels and health"), 44 (patent "monopoliz[es] all thought about the health effects of the biologic fact ... that thiopurine drugs produce metabolites that relate to the health of patients with autoimmune diseases").

for the biotechnology industry, and particularly for the types of technologies described in this brief.

Again, an example demonstrates why this is so. The study and use of "biomarkers" is essential to the treatment approaches required for personalized medicine. Biomarkers typically are naturally occurring proteins, genes, or gene transcripts that provide a "readout" on, for instance, specific disease processes within the body.[15] The presence or altered level of a particular biomarker (or relative levels of some combination of biomarkers) may be correlated with the status of a disease; an application of that correlation then may be used to diagnose patients, select appropriate therapeutic interventions, and evaluate the effect of a treatment on the course of the disease. See, *e.g.*, N. Rifai et al., *Protein biomarker discovery and validation: the long and uncertain path to clinical utility*, 24 Nature Biotechnology 971 (2006).

Using a biomarker to monitor therapy, instead of relying on traditional assessments of a patient's clinical status, offers important advantages. Among these are a much earlier indication of the therapy's effectiveness, as well as freedom from "interference" due to the progression of other diseases in the patient. Such advantages allow doctors to more effectively tailor therapeutic approaches to individual patients. In addition to the use of biomarkers to detect the presence of, or susceptibility to, certain diseases or toxins, biomarkers also may be used to

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[15] *See, e.g.*, Food & Drug Admin., *Challenge and Opportunity on the Critical Path to New Medical Products* 23 (Mar. 2004), *available at* http://tinyurl.com/6ykodwv (defining "biomarkers" as "quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness").

explain the response of individual patients to certain drugs, and to identify classes of patients who are more or less likely to benefit when treated. These technologies have implications for global public health; the United Nations, for example, has recognized that prevention and early screening, both of which can be improved through personalized medicine technologies, are key components in global strategies to lessen the rate of non-communicable diseases. See G.A. Draft Res. 66/1, ¶¶ 1-3, 17, 34, 45(k), (l), (p), (q), U.N. Doc. A/RES/66/1 (Sept. 16, 2011).

Thus, it is expected that the use of biomarkers will allow drug developers to conduct clinical trials of new medicines more quickly, more economically, and with smaller numbers of patients than are now required. Moreover, biomarker technology may enable drug developers to explain seemingly inconclusive or negative results from past clinical studies, and to identify valuable uses for some of the hundreds of investigative drugs whose clinical testing has been discontinued due to inconsistent efficacy or toxicity. Biomarker technology therefore offers hope that at least some "failed" drugs may be developed into the "right drug for the right patient," and that past investments made by patient volunteers, physicians, academic scientists and drug developers may come to fruition after all. See Roche/Abbott Br. 7-13 (discussing examples of innovations in personalized medicine that make use of biomarkers).

Biomarkers and their use in diagnosis or treatment, however, necessarily are linked to the human body's biological processes. In other words, any form of human intervention and activity that makes use of biomarkers necessarily will make use of the response of a biological system. A rule of patent law that holds these applications to be natural phenomena or

principles *per se*, and thus non-patent-eligible at the threshold, will obviate patent protection in this domain—contrary to well-settled law. As the Court explained in *Chakrabarty*, the "relevant distinction" between patent-eligible subject matter and ineligible subject matter is "not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions." 447 U.S. at 313. Thus, an invention that exploits a biological response—that, for example, involves the identification and use of biomarkers for a particular treatment or diagnostic purpose—is patentable so long as the biological response is used in the context of a broader process, with transformative steps that provides a treatment, diagnosis, or other medical function. See *Chatfield*, 545 F.2d at 158 ("We should not penalize the inventor who makes his invention by discovering new and unobvious mathematical relationships which he then utilizes in a machine, as against the inventor who makes the same machine by trial and error and does not disclose the laws by which it operates.").

The proper distinction between patent-eligible and -ineligible uses of biomarkers and biological responses was illustrated well by the Federal Circuit's analysis in the recent *Myriad* case. See *Ass'n for Molecular Pathology* v. *USPTO*, 653 F.3d 1329 (Fed. Cir. 2011) ("*Myriad*"). In *Myriad*, the Federal Circuit held to be unpatentable subject matter a claimed "method for screening a tumor sample" by "comparing" a first BRCA1 sequence from a tumor sample and a second BRCA1 sequence from a non-tumor sample, wherein a difference indicates an alteration in the tumor sample. The claim did not include the steps of extracting DNA from a human sample or sequencing the BRCA DNA molecule; instead, the

claim recited only "comparing" the tumor and non-tumor samples. *Id.* at 1356-57. The Federal Circuit therefore held the claim unpatentable: "This claim thus recites nothing more than the abstract mental steps necessary to compare two different nucleotide sequences." *Id.* at 1356.

By contrast, a claim directed to a method for screening potential cancer therapeutics via changes in cell growth rates was patentable, because the claimed method included the steps of "growing" host cells transformed with an altered BRCA1 gene in the presence or absence of a potential cancer therapeutic, "'determining' the growth rate of the host cells with or without the therapeutic," and "'comparing' the growth rate of the host cells." *Id.* at 1357-58. Because these steps involved a "physical manipulation of the cells"—i.e., a tangible transformation rather than a mere observation, as in the claim held unpatentable—they satisfied § 101. *Id.*

Similarly, in *In re Grams*, the applicant claimed a process that involved (1) performing any generic clinical test on individuals and (2) based on the data from that test, determining if an abnormality existed and determining possible causes of any abnormality by using an algorithm. 888 F.2d 835 (Fed. Cir. 1989). The Federal Circuit found that this process was not drawn to patentable subject matter because the essence of the claimed process was the mathematical algorithm, rather than any transformation of the tested individuals. *Id.* at 839-41. In particular, the *Grams* process was no more than an algorithm performed on collected data; although gathering the relevant data was a step in the claimed process, the claims did not require the performing of a specific clinical test that was shown to be transformative. As these examples illustrate, where a claimed process

does include tangible, transformative steps that limit the claim to a particular application, as the asserted claims at issue here do, the claim is patent-eligible subject matter.

Here, Petitioners seek to avoid the impact of these principles by focusing solely on the reference in the claim to the deduced relationship between 6-TG and 6-MMP following administration of the agent that creates these metabolites. But Petitioners can make this argument only by ignoring the key process steps of "administering a drug providing 6-thioguanine to a subject" and "determining the level of 6-thioguanine in said subject." These steps "are part of a treatment protocol, and they are transformative." Pet. App. 20a; see also U.S. Br. 14 ("The claim recites a series of acts in the physical world that achieve a useful end (treatment of auto-immune disorders) by transforming the body chemistry of the patient."). Once these steps are taken into consideration, it is apparent that the asserted claims recite an application of the correlation between 6-TG and 6-MMP—not the correlation itself. And, for this reason, the process for determining the plasma concentrations of metabolites produced after the administration of a manmade medication is not a "natural phenomenon." It is instead the product of human intervention, the result of administering a foreign agent (*i.e.*, the drug) and undertaking a transformative test to determine the resulting level of metabolites. A process that determines and makes practical use of these non-natural metabolite levels is not a patent-ineligible natural phenomenon.[16]

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[16] Notably, the "administering" step, entailing active transformation of both the patient and the drug and giving rise to a non-naturally occurring correlation, distinguishes the Prometheus claims from those at issue in *Laboratory Corp. of*

To accept Petitioners' argument would require ignoring these essential, non-"natural" aspects of the claimed process—eliminating the "trees" (*i.e.*, steps) of the asserted claims in a manner that would substantially transform the forest. Such an approach is inconsistent with this Court's precedents, and it poses grave risks to the biotechnology industry and the future of personalized medicine, in which known biomarkers and known correlations are frequently used in novel processes for beneficial treatment or diagnostic purposes. This Court should reiterate that "a process by which a principle is applied to effect a useful result" is patentable subject matter. *Tilghman*, 102 U.S. at 724.

America Holdings v. *Metabolite Laboratories Inc.*, 548 U.S. 124 (2006) (per curiam). The claim at issue in that case involved no more than a correlation between a naturally occurring vitamin deficiency with an elevated level of homocysteine. That claim involved no transformative steps of any kind and is thus materially distinguishable from the claims at issue here.

CONCLUSION

For the foregoing reasons, and those stated in Respondent's Brief, the judgment of the court of appeals should be affirmed.

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AMICUS CURIAE BRIEF

RECORD AND BRIEFS

No. 10-1150

In the Supreme Court of the United States

MAYO COLLABORATIVE SVCS. (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER, *Petitioners*,

v.

PROMETHEUS LABORATORIES, INC., *Respondent*.

On Writ of Certiorari to the U.S. Court of Appeals for the Federal Circuit

BRIEF OF *AMICI CURIAE* CATO INSTITUTE, REASON FOUNDATION, AND COMPETITIVE ENTERPRISE INSTITUTE IN SUPPORT OF PETITIONERS

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QUESTION PRESENTED

Whether someone can patent the process of observing correlations between blood test results and patient health—effectively preempting all uses of the naturally occurring correlations—simply because the methods used to administer prescription drugs and test blood may involve "transformations" of body chemistry.

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INTEREST OF *AMICI CURIAE*[1]

The Cato Institute was established in 1977 as a nonpartisan public policy research foundation dedicated to advancing the principles of individual liberty, free markets, and limited government. Cato's Center for Constitutional Studies was established in 1989 to help restore the principles of limited constitutional government that are the foundation of liberty. Toward those ends, Cato publishes books and studies, conducts conferences and forums, publishes the annual *Cato Supreme Court Review*, and files *amicus* briefs. This case is of central concern to Cato because it implicates an overreach of the federal power to establish patents, thus stifling free markets and infringing on individual liberty.

Reason Foundation is a national, nonpartisan, and nonprofit public policy think tank, founded in 1978. Reason's mission is to promote liberty by developing, applying, and communicating libertarian principles and policies, including free markets, individual liberty, and the rule of law. Reason promotes policies that allow and encourage individuals and voluntary institutions to flourish. Reason advances its mission by publishing Reason Magazine, as well as commentary on its websites, www.reason.com and www.reason.tv, and by issuing policy research reports that promote choice, competition, and a dynamic market economy as the foundation for human dignity

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[1] Pursuant to this Court's Rule 37.3(a), letters of consent from all parties to the filing of this brief have been submitted to the Clerk. Pursuant to this Court's Rule 37.6, *amici* state that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than *amici* or their counsel made a monetary contribution intended to fund the preparation or submission of this brief.

and progress. To further its commitment to "Free Minds and Free Markets," Reason participates as *amicus curiae* in cases raising significant issues.

The Competitive Enterprise Institute is a nonprofit, nonpartisan public interest organization dedicated to empowering individuals to make their own choices in a free market. Founded in 1984, CEI has been involved in a wide range of policy debates, from energy and economic issues to technology and medical care. CEI's interest in this case is based on our view that government efforts to "promote the progress of science and useful arts" must protect freedom of thought and preserve a rich public domain.

SUMMARY OF ARGUMENT

Prometheus's patents are two among thousands of abstract process patents which have been improvidently granted since the 1990s. The patents at issue present an opportunity for the Court to restore the original meaning of patentable "process" and reverse an expansion of patentable subject matter that has discouraged innovation and harmed U.S. industries.

The patents at issue are not "processes" as the term was understood when section 101 of the Patent Act of 1952 was adopted. The Patent Act's legislative history explains that the term "process" meant "art," as it had been used in earlier patent statutes. Patentable arts were limited to processes which aimed to produce an effect on matter, and these patents do not.

Moreover, the patents at issue here do not describe a process by either a historic or general definition of the term. A process is a series of actions, and

the "indication" element of the claims does not describe an action.

Enforcing the patents here will have a deleterious economic effect on the healthcare and medical research industries and will retard innovation. Empirical evidence shows that other abstract process patents, such as software and business-method patents, have resulted in aggregate financial losses for American firms and have discouraged rather than encouraged innovation. The effect of abstract process patents on software and financial firms will spread to the healthcare and medical research industries if patents such as Prometheus's are permitted.

Prometheus's patents will also impermissibly restrict public domain activity. These patents' final step is entirely mental. Patents whose final step is mental have the effect of transforming non-infringing, public domain activity into infringing activity for those who are aware of the thought that triggers infringement. This effect discourages the dissemination of knowledge, because access to patented knowledge places individuals in situations where they must elect to cease doing what was previously a public domain activity—such as reading the results of medical tests—or inadvertently infringe a patent.

For similar reasons, the patents at issue unconstitutionally restrict freedom of thought, by putting parties at risk of incurring damages for patent infringement when they recognize the correlations described in the patents at issue. The First Amendment protects freedom of thought and places limits on patent protections, just as it does on copyright protections. As the Court stated in *Eldred v. Ashcroft*, 537 U.S. 186 (2003), copyrights could require First Amend-

ment scrutiny if "the traditional contours of copyright protection" were altered. The patents at issue here represent an unprecedented departure from the traditional contours of patent protection; only recently have parties sought patent protection for claims which final element encompasses pure thought. Even if the patents at issue are otherwise patentable subject matter, these patents unconstitutionally restrict freedom of thought in violation of the First Amendment and should be invalidated.

ARGUMENT

I. The Patents At Issue Are Not Processes Under Section 101 Of The Patent Act

Prometheus's patents are two among thousands of abstract process patents which have been improvidently granted since the 1990s. These patents should be invalidated because they do not qualify as "processes" under 35 U.S.C. § 101.

As an historical matter, the patents at issue do not describe activity which would have qualified as a "process" when the Patent Act of 1952 was adopted. The legislative history of the 1952 Act explains that the term "process" is coextensive with the term "art," as it had been used in earlier patent statutes. Patentable arts were limited to processes which aimed to produce an effect on matter, and these patents do not.

Additionally, the patents at issue here do not describe a process by either an historic or general definition of the term. A process is a series of actions, and the "indication" element of the claims does not describe an action.

A. The Patents at Issue Are Not Processes under Section 101 because Patentable "Processes" Were Historically Limited to Those Which Aimed to Produce an Effect on Matter.

1. "Process" in the Patent Act of 1952 shares the same meaning as "art" in the Patent Act of 1793.

The meaning of the term "process" in the Patent Act is informed by the historic limitations on process and art patents. These limits show that the patents at issue here are beyond the permissible boundaries of process patents.

The Supreme Court recently considered the meaning of "process" in *Bilski v. Kappos*, 130 S.Ct. 3218 (2010). The majority opinion emphasized *Diamond v. Diehr*'s instructions that "[u]nless otherwise defined, words will be interpreted as taking their ordinary, contemporary, common meaning, . . . and [that] in dealing with the patent laws, . . . courts should not read into the patent laws limitations and conditions which the legislature has not expressed." 450 U.S. 175, 182 (1981) (quoting *Perrin v. United States*, 444 U.S. 37, 42 (1979); *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)) (internal quotation marks omitted) (discussed in *Bilski*, 130 S.Ct. at 3226).

In contrast, Justice Stevens's concurrence emphasized that the term "process" must be understood as a "complex term[ ] of art developed against a particular historical background." *Bilski*, 130 S.Ct. at 3238 (Stevens, J., concurring). Although some language in *Diehr* suggests that the term "process" can be simply

understood by its lay or dictionary definition alone,[2] the *Diehr* court also acknowledged the relationship between the terms "process" in the 1952 Act and "art" in previous patent statutes. *See* 450 U.S. at 182 ("[A] process has historically enjoyed patent protection because it was considered a form of 'art' as that term was used in the 1793 Act."); *see also Parker v. Flook*, 437 U.S. 584, 588 (1978) (explaining that a claim may describe a "'process' in the ordinary sense of the word" but still not be patentable subject matter).

The term "process" first appeared as a category for patentable subject matter in the 1952 Act, replacing the term "art" which had been a category of patentable subject matter in earlier patent statutes. The report of the Senate Judiciary Committee explained the change was cosmetic and did not alter the scope of patentable subject matter:

> "Art" [in prior patent statutes] . . . is interpreted by the courts to be practically synonymous with process or method. The word "process" has been used to avoid the necessity of explanation that the word "art" as used in this place means "process or method," and that it does not mean the same thing as the word "art" in other places [*e.g.*, sections describing "prior art"].[3]

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[2] Other categories of patentable subject matter, such as "manufacture" and "composition of matter," have been interpreted in accordance with their lay or dictionary definitions or common usage. *See Bilski*, 130 S.Ct. at 3226 (citing *Chakrabarty*, 447 U.S. at 308).

[3] The committee report also explained, "The definition of 'process' has been added in section 100 to make it clear that 'process

S.Rep. No. 82-1979, at 2398-99 (1952).

Because the change from "art" to "process" in the 1952 Act was cosmetic, the present-day meaning of "process" is substantially informed by the meaning of the term "art" in earlier patent statutes.

The Patent Act of 1793 allowed patents to issue for "any new and useful art, machine, manufacture, or composition of matter."[4] Ch. 11, 1 Stat. 318, 319. An early authority on patent law,[5] George Ticknor Curtis, described the term "art" as "a new process or method of working or of producing an effect or result in matter." George Ticknor Curtis, A Treatise on the

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or method' is meant, and also to clarify the present law as to the patentability of certain types of processes or methods as to which some insubstantial doubts have been expressed." S.Rep. No. 82-1979, at 2399 (1952). The "insubstantial doubts" language referred to dicta in *In re Thuau*, 135 F.2d 344, 347 (C.C.P.A. 1943), and other decisions that suggested a new use of a known machine, manufacture or composition of matter could not be patented. Peter S. Menell, *Forty Years of Wandering in the Wilderness and No Closer to the Promised Land*, 63 Stan. L. Rev. 1289, 1297 (2011) (citing P.J. Federico, *Commentary on the New Patent Act*, 35 U.S.C.A. 1 (West 1954), *reprinted in* 75 J. Pat. & Trademark Off. Soc'y 161, 176-77 (1993)).

[4] In his concurring opinion in *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008), Judge Dyk described how "the categories of patentable subject matter closely tracked the English approach, and in certain respects reflected a deliberate choice between competing views prevalent in England [around 1793]." 545 F.3d at 968 (Dyk, J., concurring). In the mid-eighteenth century, England had not yet resolved whether processes for manufacturing were themselves patentable under the statute. In the 1793 Patent Act, Congress resolved this question by including the term "art" in the statute. *Id.* at 970.

[5] Robert Merges & John Duffy, Patent Law & Policy 916 (3d ed. 2002) (cited in Menell, *supra*, at 1295).

Law of Patents for Useful Inventions § 9 (Boston, Little, Brown & Co. 3d ed. 1867) (cited in Menell, *supra*, at 1295). He illustrated the definition with examples drawn from case law, each of which referred to improved manufacturing techniques involving physical objects. *See id.* §§ 9-19. A later treatise by William Robinson defined "art" as "an act or a series of acts performed by some physical agent upon some physical object, and producing in such object some change either of character or of condition." 1 William C. Robinson, The Law of Patents for Useful Inventions § 159 (Boston, Little, Brown & Co. 1890). Robinson noted an "art" "is also called a 'process.'" Robinson, *supra*, at § 159 (citing *Cochrane v. Deener*, 94 U.S. 780, 788 (1876)).

Courts' interpretation of the term "process" remained in accord with the historic understanding of "art," until around the 1990s.

2. The Federal Circuit expanded the scope of patentable subject matter far beyond its historic limits throughout the 1990s.

The seeds for expanding the scope of patentable subject matter were sown in *Gottschalk v. Benson*, 409 U.S. 63 (1972). *Benson* invalidated a process patent for converting signals from binary-coded decimal into binary, emphasizing that "[p]henomena of nature, . . . mental processes, and abstract intellectual concepts [we]re not patentable." *Id.* at 67. The Court found that granting the patent "in practical effect would [grant] a patent on the [conversion] algorithm itself," *id.* at 72, and indicated that patents on software programs were beyond the scope of the patent statute. *See id.* at 72-73 ("It may be that the patent

laws should be extended to cover these programs, a policy matter to which we are not competent to speak. . . . If these programs are to be patentable, considerable problems are raised which only committees of Congress can manage.").

Following *Benson*, patent drafters attempted to redraft abstract process claims into claims for making a new machine, in the hopes of concealing any resemblance of their claims to those at issue in *Benson*.[6] *See* Robert Merges & Patrick Duffy, Patent Law and Policy 151-52 (4th ed. 2007) [hereinafter Merges &

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[6] The earliest attempt to cast a software invention as a hardware claim actually predated *Benson*. The applicant in *In re Bernhart*, 417 F.2d 1395 (C.C.P.A. 1969), filed a claim for a computer which could depict three-dimension objects in two dimensions, as opposed to filing a claim for a process of depicting three-dimensional objects *using* a computer. The Court of Customs and Patent Appeals upheld the patent, explaining that a computer with the program was, compared to a computer without the program, "a new machine."

> [I]f a machine is programmed in a certain new and unobvious way, it is physically different from the machine without that program; its memory elements are differently arranged. The fact that these physical changes are invisible to the eye should not tempt us to conclude that the machine has not been changed. If a new machine has not been invented, certainly a 'new and useful improvement' of the unprogrammed machine has been, and Congress has said in 35 U.S.C. [§] 101 that such improvements are statutory subject matter for a patent.

Id. at 1400. The tactic of recasting a process claim as a machine claim "lay dormant" until it was revived, post-*Benson*, in the 1980s. Robert Merges & Patrick Duffy, Patent Law and Policy 152 (4th ed. 2007).

Duffy 4th ed.]. This tactic succeeded when the Federal Circuit upheld machine claims for software in *In re Iwahashi*, 888 F.2d 1370 (Fed. Cir. 1989), and *In re Alappat*, 33 F.3d 1526 (Fed. Cir. 1994) (*en banc*). The Federal Circuit in *Alappat* acknowledged that "many, or arguably even all, of the means elements recited in [the claim] represent circuitry elements that perform mathematical calculations." 33 F.3d at 1544. Nonetheless, the majority concluded, "This [claim] is not a disembodied mathematical concept . . . but rather a specific machine to produce a useful, concrete, and tangible result." *Id.*

In 1998, the Federal Circuit decided *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, 149 F.3d 1368 (Fed. Cir. 1998). *State Street* eliminated the common-law ban on business-method patents, but also struggled uncomfortably with the legal fiction that software patents could be appropriately characterized as new machine claims. *State Street* attempted to gloss over the issue of whether software patents should be claimed as machines or processes. The majority claimed, "The question of whether a claim encompasses statutory subject matter should not focus on which of the four categories of subject matter a claim is directed to—process, machine, manufacture, or composition of matter—but rather on the essential characteristics of the subject matter, in particular, its practical utility." *Id.* at 1375.

Between 1994 and September 2007, the Federal Circuit held no claims unpatentable under 35 U.S.C. § 101.[7] Merges & Duffy 4th ed., *supra*, at 153-54.[8]

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[7] Notably, no appellate decisions were rendered on patentable subject matter between 1982 and 1989 either—"which strongly suggests the [Patent and Trademark Office ("PTO")] was not

During this period, the granting of software patents became the norm. Whereas only 262 software patents were issued between 1978 and 1987, the PTO issued approximately 4,500 software patents in 1994. *See* Jeffrey J. Blatt, *Software Patents: Myth Versus Virtual Reality*, 17 Hastings Comm. & Ent. L.J. 795, 816 (1995); John T. Soma & B.F. Smith, *Software Trends: Who's Getting How Many of What? 1978 to 1987*, 71 J. Pat. & Trademark Off. Soc'y 415, 418-19 (1989); Merges & Duffy 4th ed., *supra*, at 154.

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issuing rejections on that basis." Merges & Duffy 4th ed., *supra*, at 150. During those years, the PTO adopted "a liberal, rather than a conservative, interpretation of [*Diamond v. Diehr*]" and began "issuing patents for algorithms and a wide range of other software-related innovations." Pamela Samuelson, Benson *Revisited: The Case Against Patent Protection for Algorithms and Other Computer Program-Related Inventions*, 39 Emory L.J. 1025, 1094 (1990).

[8] In September 2007, the Federal Circuit invalidated patents in *In re Comiskey*, 499 F.3d 1365, 1379, 1381 (Fed. Cir. 2007) (finding claims that "describe an allegedly novel way of requiring and conducting arbitration" unpatentable under section 101), and *In re Nuijten*, 500 F.3d 1346, 1357 (Fed. Cir. 2007) (holding a signal to be unpatentable subject matter under section 101). The applicants in *In re Nuijten* argued that *State Street* rendered the four statutory categories of section 101—process, machine, manufacture, or composition of matter—irrelevant to the question of whether an invention was patentable. 500 F.3d at 1353-54. The Federal Circuit disagreed with this characterization of *State Street*, holding, "The four categories together describe the exclusive reach of patentable subject matter. If a claim covers material not found in any of the four statutory categories, that claim falls outside the plainly expressed scope of [section] 101 even if the subject matter is otherwise new and useful." *Id.* at 1354. *In re Nuijten* marked a return to focusing on the text of section 101, including the meaning of the term "process."

Because *State Street* de-emphasized the categories for subject-matter patentability, most software and business-method patents are now candidly described as processes. The proliferation of software and business-method patents represented the completion of a twofold change in patentable subject matter. Not only was the term "process" interpreted so broadly as to include processes far beyond the "arts" contemplated in the early patent acts, but the scope of the exceptions to patentable subject matter was narrowed to exclude algorithms instantiated as computer code.

3. The Court should overturn Federal Circuit precedent that broadens patentable subject matter beyond its historic limits and invalidate the patents at issue because they do not describe a "process" or "art."

The term "process" in section 101 is properly limited to processes which aim to have an effect on matter. Although software and business method patents have proliferated over the past two decades, many software and business-method patents, as well as the patents at issue here, should not qualify as patentable subject matter because the purpose of performing the processes is not to have an effect on the physical world.

Prior Supreme Court precedent is consistent with this historic understanding of patentable process. The aim of the *Diehr* patent was to cure synthetic rubber—to effect a physical change in the world—and that patent was upheld. *See* 450 U.S. at 177. In contrast the purpose of the *Benson* patent was to represent a number in binary, 409 U.S. at 64, and the purpose of the *Flook* patent was to calculate updated

alarm limits, 437 U.S. at 585. Although the algorithms in *Benson* and *Flook* would happen to effect a change on a computer, these changes did not transform the claimed algorithms into *patentable* processes because the purpose of performing the claimed processes was not to alter the physical world. The aim of the *Benson* and *Flook* patents was to represent or calculate a number, respectively. Those patents were correctly invalidated.

Similarly, the patents at issue here fail to qualify as patentable processes because the claimed processes do not aim to effect a change in the physical world. Consider, for example, Claim 1 of the '623 patent. The aim of the claim is to reveal whether levels of 6-thioguanine in a patient "indicate" that subsequent doses of a drug should be higher or lower. Recognition of whether a drug dosage should be changed is the last part of the claimed process.

The Federal Circuit observed that the patient is physically changed when the test dose of a drug is administered and that a blood sample is transformed when 6-thioguanine levels are measured. *See Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1356-57 (Fed. Cir. 2010). As with the changes in computers running the *Benson* and *Flook* algorithms, however, these changes in patients and their blood are merely side effects of the claimed process. The purpose of the patents at issue here is to reveal information about whether a drug dosage should be increased or decreased, not to change the patient's internal state or the state of blood samples.

Prometheus's claims are aimed not at producing an effect on matter, but at revealing information. They are therefore not patentable processes or art.

B. The Patents at Issue Do Not Describe a Process because a Process Is a Set of Actions and the Patents' "Indication" Step Requires No Action.

The Supreme Court and the Federal Circuit have consistently interpreted the statutory term "process" to require action. *See Benson*, 409 U.S. at 70 ("'A process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing.'" (quoting *Cochrane*, 94 U.S. at 788)); *NTP, Inc. v. Research in Motion, Ltd.*, 418 F.3d 1282, 1319 (Fed. Cir. 2005) ("'[A] process is a series of acts.'" (quoting *Minton v. Nat'l Ass'n of Sec. Dealers*, 336 F.3d 1373, 1378 (Fed. Cir. 2003))); *In re Kollar*, 286 F.3d 1326, 1332 (Fed. Cir. 2002) ("[A] process . . . consists of a series of acts or steps[9] . . . . It consists of doing something, and therefore has to be carried out or performed."); *In re Nuijten*, 500 F.3d at 1355 (explaining that a patent applicant's argument that his claims might be covered by the "process" category even if they do not recite acts "lacks merit").

The patents at issue here do not describe processes, by any dictionary or historic definition of "process," because the "indication" element does not re-

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[9] A step is "[o]ne of a series of actions, processes, or measures taken to achieve a goal." American Heritage Dictionary of the English Language 1699 (4th ed. 2000) (also defining a step as "[a] stage in a process"); *see also* Merriam-Webster's Collegiate Dictionary 1223 (11th ed. 2003) (A step is "a stage in a process" or "an action, proceeding, or measure often occurring as one in a series."); Oxford American Dictionary & Thesaurus 1281 (2d ed. 2009) (A step is "a measure or action taken to deal with or achieve something.").

quire action. *See, e.g.*, American Heritage Dictionary of the English Language 1398 (4th ed. 2000) (A process is "[a] series of actions, changes, or functions bringing about a result[,]" or "[a] series of operations performed in the making or treatment of a product."); Merriam-Webster's Collegiate Dictionary 990 (11th ed. 2003) (A process is "a series of actions or operations conducing to an end; [especially] a continuous operation or treatment esp[ecially] in manufacture."); Oxford American Dictionary & Thesaurus 1027 (2d ed. 2009) (A process is "a series of actions or steps taken toward achieving a particular end.").

Each step of a process must require someone or something to *do* something. But the final "indication" element of the claimed processes is entirely passive. Consider the final portion of Claim 1 of the '623 patent. The drug must be administered, and 6-thioguanine levels must be determined,

> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject[,] and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

2JA at 16.

This process claim allegedly has three parts: administration, determination, and indication. But the

"indication" element is not an action; it is merely an observation.

The number representing metabolite levels does not undertake the action of "indicating" anything. More accurately, the claim instructs a party reading lab results to *recognize* something about the number. But "recognizing," without doing something further based on the recognition, is not an action, and the claims in the patents at issue here, accordingly, do not describe processes.[10]

II. Enforcing The Patents At Issue Would Stifle Free-Market Competition, Slow Innovation, And Raise The Costs Of Medical Treatment

The Federal Circuit's expansive interpretation of patentable subject matter in the 1990s coincided with patents having a net negative economic effect in most industries, as the forthcoming empirical evidence shows. Broad, abstract process patents are particularly prone to litigation, the costs of which have overwhelmed the profits generated from those patents. Enforcing the patents at issue here will spread the economic harms caused by broad, abstract process patents from the software and financial industries to the healthcare industry.

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[10] Alternatively, the Court could consider the claims as only including two steps—administering the drug and determining the metabolite levels—eliminating the passive element of "recognition" from the claimed process. The administering and determining steps comprise a process according to the term's common usage, but are otherwise unpatentable as prior art.

A. The Federal Circuit's Expansive Interpretation of Patentable Subject Matter Has Hurt the Economy and Stifled Free-Market Competition.

This Court's decision in *Bilski* re-emphasized the limits on patentable subject matter. Nonetheless, the Federal Circuit's validation of the patents at issue here demonstrates that the boundaries of patentable subject matter remain far beyond their appropriate and historic limits in the Federal Circuit.

Granting highly abstract process patents not only deviates from the historic understanding of patentable processes, but also has wreaked tremendous damage on numerous sectors of the economy. This damage will extend to the medical and healthcare industries if medical diagnostic patents, such as the patents at issue, are upheld.

Despite the widely-held belief that stronger patent protection always provides greater incentives to innovate and monetize innovation, empirical economic evidence indicates that patents do not "universally spur innovation and economic growth." *See* James Bessen & Michael J. Meurer, *Of Patents and Property*, Regulation Mag. 18, 25 (Winter 2008/2009). Bessen and Meurer analyzed the costs and benefits of patenting over the past few decades and concluded that "patents may actually discourage investment in innovation" for public firms in "most industries today." *Id.*

Although patents have consistently provided a positive return on investment to chemical and pharmaceutical firms, patents have had a much more ambiguous effect in other industries. During the 1980s, public non-pharmaceutical and -chemical firms

"might have, at best, broken even from patents." *Id.* By 1994, however, the costs of litigating patents in other industries had mushroomed far beyond the profits earned from patents. *See* Patents, Profits, and Costs, *infra* App. A, at 1a (Graphs of cost of patent litigation compared to worldwide profits from patents in the 1980s and 1990s.). "By almost any interpretation, the patent system could not [have been] providing overall positive incentives for those . . . firms by the end of the 1990s." Bessen & Meurer, *Of Patents and Property*, *supra*, at 25; *see also* James Bessen & Michael J. Meurer, Patent Failure 138-42 (2008).

It is no coincidence that the patent system switched from a system which encouraged innovation to one which created economic losses in the 1990s. *In re Iwahashi* and *In re Alappat*, coupled with the PTO's willingness to grant patents on software and business methods, caused broad, abstract process patents to proliferate. Firms scrambled to acquire patents in newly available areas, either out of belief that patenting would be profitable, or defensively, to prevent competitors from acquiring broad patents that would threaten their existing projects and business models. In 1991, even Bill Gates worried that "some large company w[ould] [acquire a software] patent [on] some obvious thing" and use the patent to "take as much of [Microsoft's] profits as they want[ed]." *See* Timothy B. Lee, *A Patent Lie*, N.Y. Times, June 9, 2007, at A15.

Software and business method patents presented and continue to present numerous difficulties for firms. Critically, it is almost impossible for a firm to search through existing patents, determine when its own software is infringing existing software patents,

and license the pre-existing patents to clear the rights for its own work. Searching the patent system for patents covering material similar to one's own software can reveal thousands of patents. A recent episode of *This American Life* on National Public Radio demonstrated the problem. The program interviewed David Martin, who runs a company called M-Cam. M-Cam is hired by the government, banks, and other businesses to assess patent quality. Martin demonstrated how M-Cam's software searches existing patents and can detect overlap between then. Martin tested patent no. 5771354, a 1998 patent that covers upgrading software on one's home computer over the internet. He discovered that while the '354 patent was being prosecuted, 5,303 other patents covering the same or very similar material were issued by the PTO. *See This American Life # 441: When Patents Attack* (National Public Radio broadcast July 22, 2011), *transcript available at* http://www.thisamericanlife.org/sites/default/files/TAL441_transcript.pdf.

As software patents proliferated, patent thickets developed, making it even more impracticable for a company to acquire all of the licenses it would need to market a completely cleared product. For example, there are as many as 250,000 patents relevant to smartphones. *See* Richard Waters, *Patent Hunting is Latest Game in Tech Bubble Circuit*, Financial Times, July 27, 2011, at 15 (Inside Business section); Richard Waters, *Tech Patent Arms War Reaches New Level of Intensity*, Financial Times, March 31, 2011, at 16 (Inside Business section); *see also* Mike Masnick, *Acacia Buys Up More Smartphone Apps Patents: Watch The Patent Thicket Get Worse*, Techdirt, http://www.techdirt.com/blog/wireless/articles/

20110721/02264715188/acacia-buys-up-more-smartphone-apps-patents-watch-patent-thicket-get-worse.shtml (July 21, 2011) (depicting a graphic of twenty-eight firms involved in lawsuits concerning smartphone-related patents).

As a result, litigation costs associated with software and business-method patents skyrocketed, dwarfing the profits earned from those patents.

In 2008, software patents were more than twice as likely to be litigated as other patents. James Bessen & Michael J. Meurer, Patent Failure 22, 153 (2008). During the late 1990s, software patents alone accounted for 38 percent of the total cost of patent litigation to public firms. *Id.* at 22. Bessen and Meurer concluded that patents on business methods were nearly seven times more likely to be litigated than other patents. *Id.* at 22, 153. Patents related to financial products and services generally are litigated at a rate 27 to 39 times larger than patents in general. Josh Lerner, *The Litigation of Financial Innovations* 1 (2008), http://www.people.hbs.edu/jlerner/FinPatLit.09222009.pdf.

Participants in the software and financial industries thus face a significant risk attendant to their innovative endeavors—the potential cost of defending against patent lawsuits. In 1994, the senior vice president of Oracle Corporation, Jerry Baker, expressed the problem concisely. "Our engineers and patent counsel have advised me that it may be virtually impossible to develop a complicated software product today without infringing numerous broad existing patents." U.S. PTO Hearings on Software Patents, San Jose, CA (Jan. 26, 1994) (statement of Jerry Baker, Senior Vice President of Oracle Corporation),

available at http://www.uspto.gov/web/offices/com/hearings/software/sanjose/sj_baker.html. The risk of litigation is all but unavoidable for participants in the software and financial industries. As a result, these companies must focus resources—which could otherwise be used on research and development—on defending their businesses against patent lawsuits.

Lerner observed that some financial institutions "engaged in strictly defensive patenting." Lerner, *supra*, at 5. They patented innovations "to ensure that others did not patent them later" and "gathered patents with careful consideration of a possible counterattack should any rival accuse them of patent infringement." Lerner, *supra*, at 5.

Many software patentees also "obtain[] patents for purely defensive purposes, motivated by a fear of exclusion from markets at the hands of other patentees." Merges & Duffy 4th ed., *supra*, at 198. For example, in 1995, Oracle announced that while it opposed software patents, it had "embarked on an aggressive program to secure patents for its software products—primarily to protect itself against potential infringement claims, in the face of a sharp increase in recent years in the number of software patents issued by the PTO." Mark Walsh, *Bowing to Reality, Software Maker Begins Building a Patent Portfolio*, The Recorder, Aug. 17, 1995, at 1 (cited in Merges & Duffy 4th ed., *supra*, at 198).[11]

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[11] Since 1995, Oracle has also gone on the offensive, suing Google for violations of its patents. *See* Jessica Guynn, *Silicon Valley Titans Square Off; Oracle Sues Google over Java Technology Used in Android Mobile Devices*, L.A. Times, Aug. 14, 2010, at B2.

Similarly, Google recently acquired Motorola Mobility for $12.5 billion, after Microsoft and Apple spent $4.5 billion to purchase 6,000 patents from Nortel Networks, a Canadian telecommunications maker that filed for bankruptcy in 2009. *See* Evelyn N. Rusli & Claire Cain Miller, *Google to Buy Motorola Mobility for $12.5 Billion*, N.Y. Times Dealbook Blog, http://dealbook.nytimes.com/2011/08/15/google-to-buy-motorola-mobility/ (Aug. 15, 2011). Google's CEO Larry Page explained part of the motivation for the purchase. "[C]ompanies including Microsoft and Apple are banding together in anti-competitive patent attacks on [the smartphone platform] Android. . . . Our acquisition of Motorola will increase competition by strengthening Google's patent portfolio, which will enable us to better protect Android from anti-competitive threats from Microsoft, Apple and other companies." *See* Larry Page, *Supercharging Android: Google to Acquire Motorola Mobility*, Official Google Blog, http://googleblog.blogspot.com/2011/08/supercharging-android-google-to-acquire.html (Aug. 15, 2011). Microsoft had previously demanded that Samsung Electronics Co. Ltd. pay Microsoft fifteen dollars for each smartphone handset it makes based on Google Inc.'s Android operating system. *See Microsoft Wants Samsung to Pay Smartphone License: Report*, Reuters, http://www.reuters.com/article/2011/07/06/us-samsung-microsoft-idUSTRE7651DB20110706 (July 6, 2011).

Companies such as Oracle, Google, and Microsoft are engaged in a patent "arms race," spending fortunes to obtain enough patents to deter competitors from suing them. Small firms that can't keep up may be run out of business, but these large firms will likely find themselves in a state of "mutually assured de-

struction," in which no firm will dare to initiate patent litigation for fear of retaliation.

These firms will wind up in the same competitive position they would have been in had the patents never issued—free to compete against each other in the market without regard to patents—at a cost of billions of dollars. These billions would have been better used to improve products on the market, to bring new products to market, and to further research and development of new technology. In short, these firms are playing the prisoner's dilemma game—and they are all defecting.

This patent arms race is not a necessary cost of encouraging innovation. Indeed, most innovations would be developed even if patent protection were unavailable. Between 90 and 98 percent of modern patent lawsuits are filed against independent inventors, not copiers. Mark A. Lemley, *The Myth of the Sole Inventor* 8 (2011), *available at* http://ssrn.com/abstract=1856610 (citing Christopher A. Cotropia & Mark A. Lemley, *Copying in Patent Law*, 87 N.C. L. Rev. 1421 (2009)). Parties who infringe software and business method patents are overwhelmingly parties who have independently developed processes similar or identical to patented material, not those who have copied. The frequency of simultaneous, independent invention demonstrates that most software and business method advances would occur without patent protection, *see generally* Lemley, *Myth of the Sole Inventor*, *supra*, at 7-51, and that the costs of patenting borne by the software and financial industries are not associated with the benefit of developing new knowledge.

There is no evidence that the availability of software and business method patents create incentives for new innovations; these abstract process patents are simply not necessary to encourage new developments in the software and financial fields. The billions of dollars firms spend buying and litigating patents are truly wastes of resources, and as a result, consumers are likely to pay higher prices for less-advanced products.

B. Enforcing the Patents at Issue Will Spread the Harms Caused by Abstract Process Patents to the Medical Profession and Healthcare Industries.

Enforcing the patents at issue will spread the problems caused by abstract process patents to the healthcare industry in general and medical diagnoses in particular, placing researchers and institutions in "constant fear of litigation." *Bilski*, 130 S.Ct. at 3256 (Stevens, J., concurring). "[M]any [diagnostic] decisions, no matter how small, could be *potential* patent violations." *Id.* To avoid infringement, medical institutions and researchers would "need to undertake the costs of searching through patents" and then "decide whether their [diagnostic method] is one that remains in the public domain." *Id.*

Perversely, as this case illustrates, searching through patents would be necessary to avoid inadvertent infringement, but also could perilously open the door to infringements of patents like Prometheus's. For example, if in searching patent documents, a researcher read about the correlations in the '623 or '302 patents, her *previously uninfringing* activity—looking at metabolite levels after administering a drug—would become infringing because she would be

unable to erase the information from Prometheus's patents from her memory. Moreover, by reading the patent, researchers and institutions could subject themselves to increased liability as willful infringers. *See, e.g.*, Mark A. Lemley & Ragesh K. Tangri, *Ending Patent Law's Willfulness Game*, 18 Berkeley Tech. L.J. 1085, 1100-02 (2001) (noting that lawyers often advise engineers not to read competitor patents for fear of their becoming willful infringers); Doug Lichtman, *Substitutes for the Doctrine of Equivalents*, 93 Geo. L.J. 2013, 2023, 2023 n.42 (2005) (same).

Issuing patents on medical diagnostic techniques will result in economic harms in the healthcare industry similar to those that have been documented in the software and financial industries. Like many abstract process patents, medical diagnostic methods can often be performed and discovered by individuals or small groups. As a result, many parties may acquire patents, and even greater numbers of well-meaning parties may inadvertently infringe them, just as in the software and financial industries.

Permitting patenting of medical diagnostic methods may also "inhibit doctors from using their best medical judgment; . . . force doctors to spend unnecessary time and energy to enter into license agreements; . . . divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations; [and] raise the cost of health care while inhibiting its effective delivery." *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 138 (2006) (Breyer, J., dissenting).

Diverting resources to litigation and avoiding patent infringement in the healthcare and medical research industries will have not only a significant eco-

nomic cost, but a human cost as well. The Court should not allow the vast harms from broad and abstract process patents to persist and spread, particularly when human health is at stake.

III. The Patents At Issue Impermissibly Remove Existent Knowledge From The Public Domain And Restrict Public Domain Activity

This Court stated in *Graham v. John Deere Co. of Kansas City* that "Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available." 383 U.S. 1, 6 (1966). But that is precisely what the patents at issue here accomplish.

Because medical diagnostic patents such as those at issue here and in *Lab Corp* are infringed when a party *recognizes* a correlation or situation, they have the potential to swallow huge swaths of otherwise public domain medical activity and research, even that which has little to do with the subject of the patent. Dr. Rokea el-Azhary's situation is simply one example of how upholding the patents at issue here would prevent unrelated research and treatment.

A patent on another recent discovery could have had even broader effects. It was recently discovered that gum disease is a risk factor that can be used to predict cardiovascular disease. An ordinary dentist who looks in a patient's mouth and notices the presence of gum disease can "correlate" in his mind the presence of gum disease with a patient's increased risk of heart attack. *See* Kevin Emerson Collins, *Constructive Nonvolition in Patent Law and the Problem of Insufficient Thought Control*, 2007 Wis. L. Rev. 759, 760 (2007) (citing Robert Genco et al., *Periodon-*

tal Disease and Cardiovascular Disease: Epidemiology and Possible Mechanisms, 133 J. Am. Dental Ass'n, June 2002, at 14S). If this diagnostic method had been patented, much common dental work and research could have become infringing for those who knew the correlation.[12]

Patents whose final step is entirely mental have the effect of transforming non-infringing, public domain activity into infringing activity for those who are aware of the thought that triggers infringement. This effect discourages the dissemination of knowledge, because access to patented knowledge places individuals in situations where they must elect to cease doing what was previously a public domain activity—such as reading the results of medical tests—or inadvertently infringe a patent.

Disclosure of new technologies is "the ultimate goal of the patent system," *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 151 (1989), but medical diagnostic patents frustrate that purpose by necessitating that the content of the patent be kept secret from those who might need to perform the

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[12] Whether the Federal Circuit would continue to find this discovery to be patentable subject matter is not certain after *Ass'n For Molecular Pathology v. U.S. Patent & Trademark Office*, 2011 WL 3211513, at *22 (Fed. Cir. July 29, 2011). As discussed by petitioners, the Federal Circuit's attempt to distinguish between the patentability of the patents at issue here and the patents in *Molecular Pathology* is strained and inconsistent with this Court's precedents. *See* Pet. Br. at 39-40. Regardless, the correlation between gum and cardiovascular disease suggests that many simple correlations between natural phenomena may yet be discovered and patented if the Court does not invalidate the patents here.

non-mental steps of the patent for other, public-domain purposes.

Upholding the patents at issue here would "confer power to block off whole areas of scientific development," creating a kind of "monopoly of knowledge" that was not the intent of Congress. *Brenner v. Manson*, 383 U.S. 519, 534 (1966). Patents must not be allowed to fence off public domain activity because of what individuals may inadvertently think about after doing those acts.

IV. Enforcing The Patents At Issue Here Would Violate The First Amendment Freedom Of Thought

A. The First Amendment Protects the Freedom of Thought.

The government cannot regulate mere thought. *See Paris Adult Theatre I v. Slaton*, 413 U.S. 49, 67-68 (1973). The Court has repeatedly recognized that the First Amendment protects freedom of thought as well as freedom of speech. *See Stanley v. Georgia*, 394 U.S. 557, 565-66 (1969) ("[T]he right to control the moral content of a person's thoughts . . . is wholly inconsistent with the philosophy of the First Amendment. . . . [The government] cannot constitutionally premise legislation on the desirability of controlling a person's private thoughts."); *United States v. Ballard*, 322 U.S. 78, 86 (1944) ("Freedom of thought . . . is basic in a society of free men."); *see also Wallace v. Jaffee*, 472 U.S. 38, 51 (1985) (acknowledging that freedom of thought is protected by the First Amendment); *Wooley v. Maynard*, 430 U.S. 705, 714 (1977) (same). Recently, the Court, in *Ashcroft v. Free Speech Coalition*, explained, "First Amendment freedoms are most in danger when the government seeks

to control thought or to justify its laws for that impermissible end. The right to think is the beginning of freedom . . . ." 535 U.S. 234, 253 (2002).

Enforcing the patents at issue here would violate individuals, such as Dr. el-Azhary's, freedom of thought. Before learning of the correlations described in the claimed patents here, Dr. el-Azhary was able to administer drugs and determine the amount of metabolites in patients without risk of patent infringement.[13] Only upon learning the correlations—and presumably thinking about them when she sees the metabolite levels of her patients—did she put her and Mayo's interests at risk. By forcing Mayo, or any party not covered by 35 U.S.C. § 287(c), to pay damages for infringing the patents at issue here, the government engages in punishment for mere thought.

B. Patents Granted under the Progress Clause Are Subject to First Amendment Scrutiny.

Enforcing the patents at issue here constitutes a content-based regulation of thought. Even in light of the limited role of the First Amendment in the context of copyright, as articulated in *Eldred v. Ashcroft*, 537 U.S. 186 (2003), the patents at issue here should

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[13] Dr. el-Azhary conducted a study on patients suffering from autoimmune diseases of the skin. She prescribed thiopurine and collected data on patients' metabolite levels to establish a therapeutic range for dermatological disorders. *See* 1JA 17-18. Dr. el-Azhary testified that Prometheus's gastrointestinal-related metabolite levels were "irrelevant to [her] study" because "there [wa]s no reason to extrapolate [their findings] to dermatology." 1JA 19. Nonetheless, once she learned Prometheus's correlations, she could not help but infringe the patent while conducting what would have otherwise been non-infringing research.

be invalidated as an unprecedented content-based regulation of thought that ventures far beyond the traditional contours of patent protection.

The *Eldred* court articulated a limited role for the First Amendment in copyright law. "The [Progress] Clause and First Amendment were adopted close in time. This proximity indicates that, in the Framers' view, copyright's limited monopolies are compatible with free speech principles. . . . [C]opyright's build-in free speech safeguards [such as fair use and the idea/expression distinction] are generally adequate to address [First Amendment concerns]." *Id.* at 219, 221.

Nonetheless, copyright law could still run afoul of the First Amendment. The Court noted that copyrights were not "categorically immune from challenges under the First Amendment." *Id.* at 221 (internal quotations omitted). Where Congress "alter[s] the traditional contours of copyright protection," First Amendment scrutiny may be necessary. *Id.*

Speech plays a very different role in patents and copyrights. Copyright law inherently restricts the dissemination of copyrighted materials that would otherwise constitute protected First Amendment activity. The *Eldred* majority's observation that the Framers must have viewed "copyright's limited monopolies" as "compatible with free speech principles" is understandable.

In contrast, patents generally do not raise First Amendment issues. Patent applicants must disclose their inventions to be awarded a patent, and those disclosures are made public and may be widely disseminated. Patent law has not developed the "free speech safeguards" of copyright law because patent

law does not usually exist in tension with First Amendment freedoms.

Because patent law lacks the "free speech safeguards" of copyright law, the patents at issue here should be subject to strict scrutiny because enforcing them places individuals who think particular thoughts, after doing otherwise non-infringing activity, at risk of punishment.

Even if patent law is subject to the limited First Amendment protections described in *Eldred*, these patents should be invalidated. *Eldred* specified that copyrights could require First Amendment scrutiny if "the traditional contours of copyright protection" were altered. *Id.* The patents at issue here represent an unprecedented departure from the traditional contours of patent protection. Patents have traditionally protected *objects* and *actions*.[14] Only recently have parties sought patent protection for claims which final element encompasses *pure thought*. The patents at issue here extend far beyond the traditional contours of patent protection and have frightening First Amendment implications. Even if they cover otherwise patentable subject matter, the claimed patents should be invalidated as unconscionable violations of the freedom of thought.

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[14] The objects may be animate or inanimate. *See, e.g., Chakrabarty*, 447 U.S. at 310.

CONCLUSION

Thomas Jefferson, the author of the Patent Act of 1793, was one of the key framers of this country's intellectual property jurisprudence. In 1966, the Supreme Court thus characterized his views on the subject:

> [Jefferson believed] [t]he patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge. The grant of an exclusive right to an invention was the creation of society—at odds with the inherent free nature of disclosed ideas—and was not to be freely given.

Graham, 383 U.S. at 8-9.

Enforcing the patents at issue here will not "bring forth new knowledge." *Id.* at 9. Instead, it would further an improvident and unconstitutional expansion of patentable subject matter which has primarily served to slow rather than to spur innovation.

Continuing on this path by permitting medical-diagnostic patents will only serve to further slow the economy, retard technological innovation, distort the free market, and place human health at risk.

The Federal Circuit's judgment should be reversed.

Respectfully submitted.

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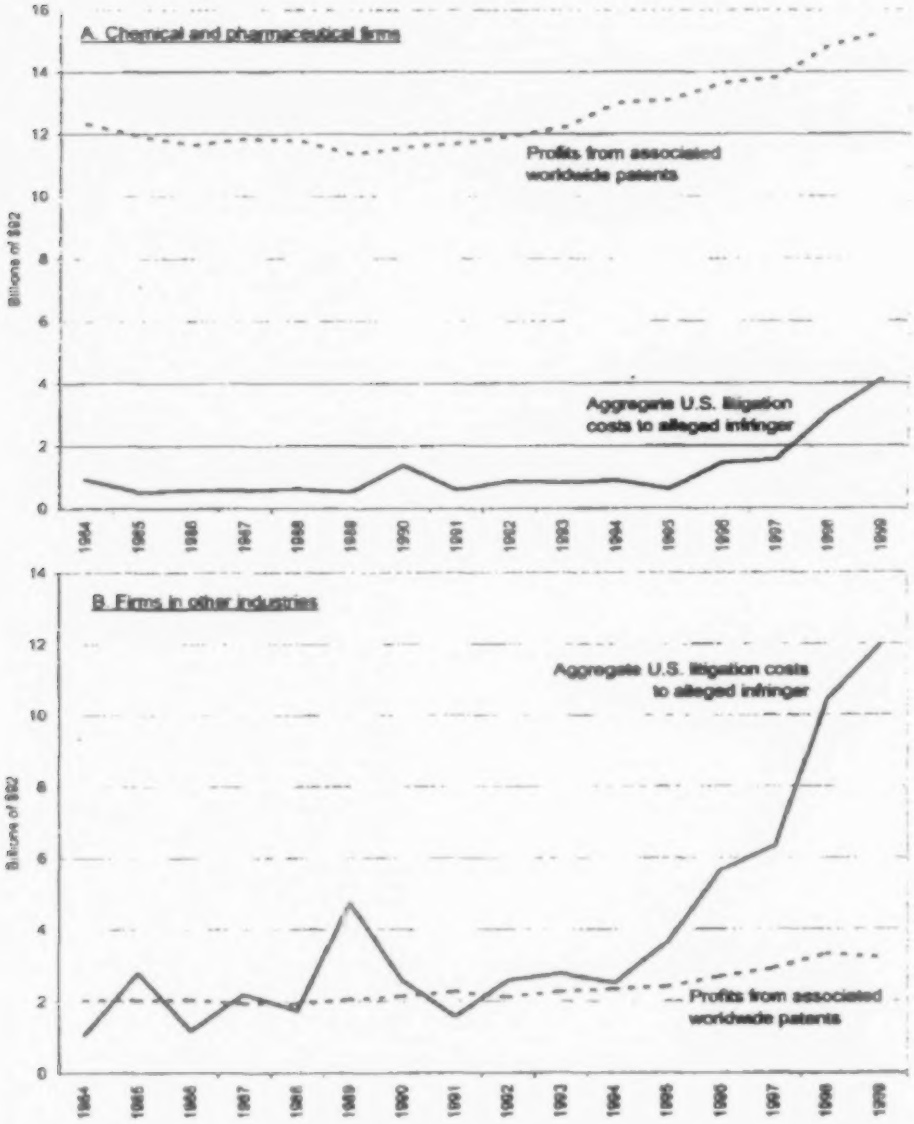
APPENDIX A

Patents, Profits, and Costs

Aggregate profits from patents and aggregate litigation costs for U.S. public firms.



James Bessen & Michael J. Meurer, *Of Patents and Property*, Regulation Mag. 18, 25 (Winter 2008/2009).

AMICUS CURIAE BRIEF

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES)
AND MAYO CLINIC ROCHESTER,
Petitioners,

vs.

PROMETHEUS LABORATORIES, INC.,
Respondent.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICI CURIAE* CONNECT AND SAN DIEGO INTELLECTUAL PROPERTY LAW ASSOCIATION IN SUPPORT OF RESPONDENTS

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QUESTION PRESENTED

The Patent Act, in 35 U.S.C. §101, states that "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof" is eligible for patent protection if it meets the other conditions for patentability required under the patent code.

The question presented is:

Whether the Federal Circuit correctly held that claims with elements that satisfy the "machine or transformation" test for patentability under §101 are patent eligible if an element of the claims includes an "application of naturally occurring correlations between metabolite levels and efficacy or toxicity" of a metabolite of a drug that provides 6-thioguanine.

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MISCELLANEOUS

D. Crouch and R. Merges,
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STATEMENT OF INTEREST OF *AMICUS CURIAE*[1]

CONNECT was created in 1985 by the City of San Diego and the University of California, San Diego, to stimulate commercialization of discoveries from local research institutions through education, mentoring, and by fostering a "culture of collaboration" between the research organizations, industry, capital sources, and professional service providers. CONNECT has assisted in the formation and development of more than 2,000 companies, and is regarded as one of the world's most successful and emulated regional programs linking investors and entrepreneurs with the resources they need for commercialization.

Founded with the specific goal of helping inventors and entrepreneurs to understand and overcome the numerous obstacles faced by new technology-based ventures, CONNECT views with heightening concern the rising cost and complexity of obtaining and enforcing patents on cutting edge technologies. CONNECT is also well positioned to render an objective assessment of

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1 Pursuant to Supreme Court Rule 37.6, SDIPLA and CONNECT state that this brief was prepared by members of the SDIPLA Amicus Committee and the CONNECT Public Policy Committee on a *pro bono* basis. Counsel for a party did not author this brief in whole or in part. Nor did counsel for a party make a monetary contribution intended to fund the preparation or submission of the brief. In addition, all parties have consented to the filing of this *amicus* brief, and their consent letters are on file with the Clerk's office.

the effect that uncertain patentability has on the ability of a struggling new company to raise capital, particularly in the economic climate prevailing today, in the period between when a patent application is filed and its ultimate disposition in the United States Patent & Trademark Office.

Therefore, it is especially troubling to CONNECT that the jurisprudence underlying 35 U.S.C §101 has evolved and continues to evolve in a manner that makes it difficult, particularly, it seems, in the case of pioneer technologies, to determine at the very threshold of the patenting process, whether the claimed invention is a "useful process, machine, manufacture or composition of matter" within the meaning of the statute.

CONNECT appreciates that inventors starting new ventures take significant professional and financial risks when leaving established jobs, investing personal savings, and filing patent applications to help capture the value of their technology. Confidence of potential investors that their inventions are eligible for patent protection is one of the most important of the criteria which must exist if inventors are to secure financial backing. Such outside investment mitigates the personal risks that inventors take in starting up new technology-based businesses that "promote the Progress of Science and useful Arts."

Because the availability of patent protection is a *sine qua non* on the checklist for investors in most if not all biotechnology and high technology ventures, it is important that there exist as few legal uncertainties as possible when potential investors attempt to assess their risks. Accordingly CONNECT believes that the clarification and simplification of the legal principles underlying the application of §101 to the threshold determination of patent eligibility is of signal importance.

Such clarification and simplification would reduce the burden of determining whether to seek patent protection, reduce the PTO's burden in applying the statute to cutting edge technologies and lend greater certainty to the presumption of validity that attends all patents. Such improvements would necessarily reduce the cost associated with obtaining and enforcing patents as well as the costs and risks of investment in new technologies, benefitting not only innovators and investors, but also the public who stands to reap much of the benefit of that investment.

The San Diego Intellectual Property Law Association (SDIPLA) is a non-profit association whose members have significant ties to San Diego's world-class research institutions, and leading wireless, biotechnology, and solar industries. Comprising about 500 registered members, the SDIPLA has grown to become one of the largest intellectual property bar organizations in the country. The primary goal of the SDIPLA in serving the San Diego community

is providing continuing legal education services to its members. Today San Diego is home to almost 6,000 technology companies employing almost 140,000 people. The SDIPLA shares CONNECT's concerns regarding the burden on innovation represented by the uncertainty attending application of §101 jurisprudence and, on behalf of its members and their clients, would welcome clarification of the standards to be applied in determining threshold patent eligibility.

SUMMARY OF ARGUMENT

This case requires the Court, for the second time in less than two years, to determine whether particular process claims satisfy the patent eligibility standards required of patentable processes under 35 U.S.C. §101. The claims of the patent before the Court in this case are very straightforward. Using claim 1 of U.S. Patent No. 6,355,623 as representative of the claims before the court, as did the Federal Circuit in reaching its decision below, it can be seen that the patented method is a process for treating an immune-mediated gastrointestinal disease that requires administration of a drug that provides 6-thiopurine as an active agent. The method also requires that the level (amount) of 6-thioguanine be determined after administration of the drug. The purpose of this determination is to provide information useful for the treatment of the

patient. There can be no doubt that these two elements of the claim are patent eligible.[2]

The huge body of issued United States patents contains many examples of patents in which drugs are administered to subjects for therapeutic purposes and many examples of patents for determining the presence of analytes of interest in diagnosing or following the course of disease in human subjects. It is, therefore, almost certainly the case that, if the appealed claims contained only those elements, §101 would not be in issue because of their unexceptional nature. Instead, other issues more commonly raised in patent cases would likely be before the Court. Thus, it would be asked to determine whether the claims meet substantive requirements such as novelty, nonobviousness and enabling disclosure under §§ 102, 103 and 112 or whether there are defects in the prosecution of the patents containing those claims.

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2 For the sake of clarity, being "patent eligible" under §101 should not be taken to mean or infer that a claim is actually patentable. It merely means that the claim reads on an invention for which patent protection can be granted if other substantive conditions of the patent statute are satisfied. Apparently satisfaction of these other conditions of patentability by the claims before the Court was not determined below by the trial court that granted summary judgment on the §101 issue. Accordingly, the usual questions of novelty, nonobviousness and enablement were not before the Federal Circuit and are not before this Court. Neither CONNECT nor SDIPLA take a position whether the claims before the Court satisfy such other conditions.

The claims are before the court only because of a third element, i.e., that the measured amount of 6-thioguanine is used to indicate whether the amount of drug administered is within or outside the optimal dose. This information is important for at least two reasons. Too large an amount of the drug and its metabolites can be toxic to the subject and too small a dose might be ineffective.

The question before the Court then becomes whether this additional element makes an otherwise patent eligible claim ineligible for patent protection.

The Court most recently addressed patent eligibility under §101 in *Bilski v. Kappos*, 130 S. Ct. 3218 (U.S. 2010) in which it affirmed the judgment of the Federal Circuit but overruled its holding that only processes which meet the "machine-or-transformation" test are eligible for patenting. The invention in *Bilski* related to a "business method." Although the Court overruled the lower court's reliance on the machine-or-transformation test as the sole test for patent eligibility of process claims, it affirmed the judgment of invalidity based on its determination that the claims directed to the hedging strategy were drawn to an abstract idea. Abstract ideas, along with natural phenomena, laws of nature are among the fundamental principles that have been determined to be ineligible for patent protection. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). See also *Bilski*, 130 S. Ct. at 3225.

In *Diehr*, the Court was considering patent eligibility under §101 with respect to process claims drawn to a conventional process for curing rubber in a mold in which a computer implemented mathematical equation was used to calculate the optimum time in the mold. The Court held that, although the claim required use of a mathematical formula, it was not a claim to the formula itself. In other words it did not preempt the formula. Instead, the Court, at 450 U.S. 175, 192, upheld the validity of the claim stating that:

> "...when a claim containing a mathematical formula implements or applies that formula in a structure or process, which considered as a whole, is performing a function which the patent laws were designed to protect (e.g. transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of 101."

In determining that the claims of the patents now before the court are not invalid for being patent ineligible, we submit that the Federal Circuit specifically relied upon and applied the same reasoning as did this Court in *Diehr*. See *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F. 3d 1347, 1354-55 (Fed. Cir. 2010).

A rule of general application that can be extracted from *Diehr* is reflected in the Federal Circuit's decision below. This rule is that when a claim to a process has elements that meet the well established machine-or-transformation test it is deemed to satisfy the requirements of §101 even if it contains a specific application of one of the fundamental principles. Adoption of this test is consistent with the Court's oft stated view that the scope of §101 is broad and subject only to the narrow exceptions relating to preemption of fundamental principles. [3]

All inventions are based on or incorporate laws of nature, natural phenomena or, in some cases perhaps, abstract ideas. However, application of the rule advanced by *Amici* will not result in the preemption of any fundamental principles and, consistent with the Court's pronouncements over the past 20 years, merely permits their application in situations where their use is strictly bounded by conventional claim limitations. Importantly, a clear rule such as we are proposing will not mean that all process claims will be patentable. Some will not satisfy the machine-or-transformation test and, as in *Bilski*, will have to be evaluated using other criteria to determine whether they are directed to an abstract idea, as was the claim to a business method in *Bilski*, or preempt a natural phenomenon or law of nature. Nevertheless, we

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3 See, for example, *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)

submit that many, and perhaps the great majority of cases not involving business methods, will be resolvable by application of this rule.

Adoption of the rule proposed by *Amici* will, therefore, provide a legal structure in which it can be more easily determined that a claim is statutory, thus reducing the cost and uncertainty arising in the initial pursuit of patent protection, simplifying the examination process in many situations, and reducing the cost of and complexity of litigating patents on the cutting edge of technology. All of these results will ultimately benefit not only the inventor and investors, but also the public by providing a climate where better informed decisions to develop and bring new technology to the market can be made.

ARGUMENT

I. THE COURT SHOULD ADOPT A RULE THAT A CLAIM THAT MEETS THE MACHINE-OR-TRANSFORMATION TEST IS PATENT ELIGIBLE UNDER 35 U.S.C. §101

The determination of whether claims in a patent application undergoing examination or the claims in a patent being litigated are patent eligible turns on the construction of 35 U.S.C. §101 which provides:

> Whoever invents or discovers any new or useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Many sections of the patent statute were born with a judicial gloss arising from decisions of the courts, and particularly decisions of this Court, which in many instances preceded their enactment by many years. Accordingly, statutory language which might appear to be clear on its face might instead be highly nuanced because of such judicial gloss. So it is with §101.

This case, in part because its facts are relatively straightforward, presents the Court with an ideal and timely opportunity to substantially accomplish what has been an elusive goal since at least 1876. Specifically, the Court can simplify and bring greater clarity to the law applicable to the patent eligibility of the many permutations of processes inventors may bring forth, particularly when the claim in question applies a fundamental principle such as a law of nature or a mathematical formula to a known structure or process. Such welcome clarification will result if the Court deems a process claim to be patent eligible under §101 if it meets the machine-or-transformation test, even if the claim contains a recitation applying a fundamental principle to a known process.

As usually expressed, the machine-or-transformation test permits a determination that a process claim is patent eligible if "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." See *In re Bilski*, 545 F.3d 943, 959, 960 (Fed. Cir. 2008), aff'd, *Bilski v. Kappos*, 130 S. Ct. 3218 (2010). Although it overruled the Federal Circuit's holding in *Bilski* that the machine-or-transformation test was the sole test to be applied under §101 when determining the patent eligibility of process claims, the Court unequivocally recognized that the test retains vitality as "a useful and important clue...for determining whether some claimed inventions are processes under §101." See *Bilski*, 130 S. Ct. at 3227. Accordingly, the test also remains available for testing whether process claims that apply laws of nature, natural phenomena or other fundamental principles to known processes are patent eligible.

Amici submit that the clarification and simplification of the law of patent eligibility that would result by adopting the rule that a process claim that satisfies the machine-or-transformation is deemed patent eligible does not require any radical or even significant reinterpretation of the law applicable to patent eligibility under §101, nor must prior precedent be overruled It merely requires that the Court provide guidance to the lower courts and the Patent and Trademark Office concerning the proper application of its existing precedents.

Therefore, we turn first to a brief review of the Court's most relevant precedents.

II. THE DEVELOPMENT OF THE LAW RELEVANT TO PROMETHEUS' CLAIMS

In *Cochrane v. Deener*, 94 U.S. 780 (1876), decided in an era when there was doubt that a process not tied to a specific machine was patentable, the Court firmly resolved that doubt by affirming the validity of a patented process that the patentee claimed was "not limited to any special arrangement of machinery" *Id.* at 785. In support of its decision, the Court provided a definition of a patent-eligible process that has figured significantly in its jurisprudence affecting patent eligibility ever since. Thus, the court said:

> A process is a mode of treatment of certain materials to produce a given result. It is an act, or series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing. If new and useful, it is just as patentable as is a piece of machinery."

Id. at 788.

Even though §101 itself and cases like *Cochrane* and its progeny suggest that patent eligibility is broadly available to inventors, the Court long ago attached an important limitation

on the patentability of "inventions" which, though not specifically expressed in Section 101, has continuing vitality today. That limitation is that, notwithstanding the plain language of Section 101, laws of nature, physical phenomena and abstract ideas *per se* should be available to all and are not patentable in any form including in claims to processes that preempt all uses. See, for example, *Bilski*, 130 S. Ct. at 3225.

The Court established this exception long before the enactment of Title 35, and at least as long ago as 1852 in *Le Roy v. Tatham* 55 U.S. 156, holding:

> "[A] principle is not patentable. A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right."

Id. at 174-75.

The Court did go on to say, however, that processes that utilize such "natural agencies" are patentable. In the Court's words, with reference to these natural agencies, "the invention is not in discovering them, but applying them to useful objects." *Id.* at 175.

A similar result was reached the next year in *O'Reilly v. Morse*, 56 U.S. 62 (1853). The patent involved in that action was one of Morse's relating to the telegraph. Claim 8 of that patent,

was seen by the Court as patenting electromagnetism itself, obviously a natural phenomenon, as opposed to patenting a specific application of that phenomenon. If a patent were allowed to be granted on the phenomenon itself, this would permit an inventor to preempt all uses of a law of nature.

Thus, over time, it has become generally accepted that claims to processes that are performed by machines or cause physical transformations are patentable but process or other kinds of claims that would preempt fundamental principles such as laws of nature, naturally occurring products, mathematical equations and other natural phenomena or abstractions could not be patented. However, as this law has developed, it has also become accepted that claims to inventions which make practical application of fundamental principles can be patent eligible. Thus, in *Diehr*, this Court, in a decision holding that a process claim employing a mathematical equation was patent eligible under §101, reasoned that "an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187.[4]

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4 The Court's most recent analysis of patent eligibility in *Bilski* did not in any way modify or qualify its holding in *Diehr*. Instead the Court cited *Diehr* with approval and as offering support for its holding that the claims in *Bilski* did not meet the requirements of §101. See 130 S. Ct. at 3226.

The Federal Circuit, in reaching its decision below, analyzed the claims of the Prometheus patents in light of this court's pronouncements in *Diehr* and, in our view, reached the only determination available to it consistent with this Court's holding in *Diehr, i.e.*, that the claims are patent eligible. If the Federal Circuit's decision was correct, this conclusion begs a comparison between the claims in *Diehr* and the claims of Prometheus' patents in light of the §101 analysis applied to the *Diehr* claims.

III. A COMPARISON OF THE DIEHR AND PROMETHEUS INVENTIONS

A. The Law As Applied In *Diehr* And Applicable To The Claims of Prometheus.

It was just over 30 years ago that this Court rendered its decision in *Diamond v. Diehr*. 450 U.S. 175 (1981). For those with appropriately long memories it will perhaps be recalled that this decision was the third in a trilogy of cases decided over a decade in which the Court wrestled with the extent to which the patent law could accommodate processes that included computer implemented steps. See *Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584 (1978) and *Diehr*, 450 U.S. 175. During this busy decade, the Court also heard another §101 case, *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), in which it determined, in effect, that living human engineered cells were patentable under §101 even

though they were derivatives of natural products. In its opinion the Court noted that the legislative history to §101 indicated it was to have a broad scope as Congress considered "anything under the sun that is made by man" to be patent eligible. *Chakrabarty*, 447 U.S. at 309.

The invention claimed in *Benson* was for a method of converting binary coded decimal numbers to pure binary numbers using a general purpose computer. The claims were held to be invalid under a §101 analysis on the ground that the practical effect of the claim was to preempt the mathematical formula used for the conversion which would amount to a patent on the algorithm itself. See *Benson*, 409 U.S. at 72.

The invention claimed in *Flook* was for monitoring the operation of a catalytic process for the production of hydrocarbons that used an algorithm applied to collected data to update an alarm value. Over a strong dissent by the nucleus of the forthcoming majority in *Diehr*, the patented invention was held to be invalid under §101 because the steps of the catalytic process for production of hydrocarbons were known to the prior art and the Court deemed its decision in *O'Reilly v. Morse*, *supra* to require it to treat the algorithm as known itself. From this it reasoned that the patentee's application "considered as a whole, contains no patentable invention." See *Flook*, 437 U.S. 594-95. The decision in *Flook* is frankly difficult to square with other decisions of this Court and appears to conflate novelty of an invention with patent eligibility. This may have

occurred because the determinations of patent eligibility and novelty were not clearly separated in decisions that influenced the holding in *Flook* but preceded the enactment of the current patent law.

The invention in *Diehr*, as already noted, is for a process for curing rubber in a mold. The optimal curing time of rubber depends on a number of parameters including the temperature of the mold. The patentee claimed a process for curing rubber that appeared to be conventional except for the use of a mathematical algorithm to determine the optimum residence time in the mold. The claim was found to have met the requirements of §101. In reaching that decision the Court noted "[i]t is now commonplace that an application of a law of nature or mathematical to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187.

It is also significant that in *Bilski* the Court noted that the *Diehr* decision that application of a law of nature or mathematical formula to a known structure or process can be patent eligible was a limitation on the principles articulated in *Benson* and *Flook*. *Bilski*, 130 S. Ct. at 3230. Accordingly, it appears that the Court in both *Diehr* and *Bilski* took pains to dispel any notion that to claim the application of one of the fundamental principles to a known process is not permitted under the statute. In particular, it would be inappropriate to conflate the requirements for patent eligibility imposed by

§101 with the novelty requirement of §102. See *Diehr*, 450 U.S. at 189-90.

B. The Prometheus Claims Are Patent Eligible.

As noted in the SUMMARY OF ARGUMENT, The Federal circuit considered Claim 1 of Prometheus U.S. Patent No. 6,355,623 to be representative of the claims held invalid in the summary judgment rendered by the District Court. That claim reads as follows:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder;
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Inspection of the text of claim 1 plainly demonstrates that step (a) of the claim calls for the affirmative step of administering a drug that provides 6-thioguanine to a subject. Administering drugs to subjects to treat disease is a common feature of therapeutic patents that claim methods of treatment. It should, therefore, be beyond dispute that administering a medicine should be considered to meet the transformation prong of the machine-or-transformation test, and the Federal Circuit so held. *Prometheus*, 628 F.3d at 1356. Nor can the administration step be considered to be merely incidental to the claimed process which, after all, is directed to a therapeutic method employing the administered drug.

Similarly step (b) requires determining the level of the 6-thioguanine. Again, determining the level of an analyte in a subject is a very common feature of patent claims for analytic assays. Thus it is not surprising that the Federal Circuit found this step to be transformative as well. *Id.*, at 1357. Indeed, it would be a huge surprise to patent practitioners if analytical processes did not meet the machine-or-transformation test even though claims to many such procedures omit any reference to the

apparatus upon which they depend or call out the transformative steps upon which they are based (as was the case in *Cochrane).*

The balance of claim 1 recites the inference to be drawn from the determination of the level of 6-thioguanine in the subject after administration of the drug, i.e., whether the amount of 6-thioguanine "indicates" that the amount of drug administered is in the optimal range or above or below that range, thus informing the physician that the amount of drug should be maintained, increased or decreased.

Many patents to analytical methods include a conclusion that flows from information gathered using the method. For example, claim 14 of U.S. Patent No. 5,160,701 is a claim to a diagnostic method in which the reagents interact to form a visible result that "indicates" a positive result. Similarly, U.S. Patent No. 5,714,489 claims a method for determining whether samples taken from humans contain a target substance of medical interest by generating a color at a test site "indicative" of the substance of interest. Other analytical patents rely on the detection of radioactive isotopes to indicate the presence of an analyte. The holders of such patents would rightly be alarmed if claims including such provisions were deemed unpatentable because they employ a law of nature or natural phenomenon, for example, color or radioactivity, as an indicator of a positive result .

In short, the inclusion in the claim of an inference to be drawn from the determination of the level of 6-thioguanine in the subject should be considered to be either or both of (i) an unexceptionable or routine practice in claiming process inventions in the analytical/diagnostic arts or (ii) the application of a fundamental principle such as a law of nature to a process meeting the machine-or-transformation test that is deserving of patent protection.[5]

Such a finding would be completely consistent with the *Diehr* prescription that when a claim contains a fundamental principle (specifically in that case a mathematical formula,) and implements or applies the principle in a structure or process, "which considered as a whole, is performing a function which the patent laws were designed to protect (e.g. transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of 101." *Diehr*, 450 U.S. at 192. In this case it cannot be disputed that the claimed process for a method of treatment is a function which the patent laws were designed to protect.

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5 Again, a conclusion that a process is patent eligible under §101 does not mean the claims are patentable. The claims must still clear substantive patent law hurdles, such as utility, novelty, and nonobviousness.

IV. THE HOLDING IN *DIEHR* IF APPLIED TO PROMETHEUS' CLAIMS PERMITS SYNTHESIS OF A STRAIGHTFORWARD RULE CONCERNING SATISFACTION OF THE REQUIREMENTS OF §101.

Amici submit that the holding in *Diehr* should inform the application of §101 to the patent claims under review in this case. Thus, any process claim that meets the machine-or-transformation test, even if it recites an application of a fundamental principle to a known process, satisfies the requirements of §101. This test requires that the process either be tied to a specific machine or apparatus or transform the subject to which it is applied. Obviously, a claim so limited can never be considered to cover an abstract idea. Further, the qualifying machine or transformation elements of the claim assure that the fundamental principle, whatever form it takes, will be bounded by those elements so that such a claim cannot preempt all applications of the fundamental principle. Hence the prohibition on claims that preempt natural laws, natural phenomena and abstract ideas is never breached by such a claim.

To illuminate this foregoing point, consider a hypothetical process claim before and after language relating to a fundamental principle is added. Assume that without that language, the claim recites steps that are transformative, thereby raising no issues under §101. Obviously

it would be infringed by unauthorized practice of the claimed invention even if the user applied a fundamental principle to the process. Thus, after the addition of the language relating to the fundamental principle, the claim is actually narrower than before; i.e., it contains an additional limitation or requirement. No one has proposed, nor should they, that the unmodified claim is unpatentable under §101, because of its scope even though it is broader than the modified claim.

Thus, the claim not limited to use with the fundamental principle would actually be infringed by practice of the process using that principle. For example, if the claim to curing rubber that was the subject of the holding in *Diehr* was patentable without the inclusion of the algorithm for determining the optimal curing temperature and was practiced without license by other than the owner, the claim would be infringed by use of the process with the algorithm. Accordingly, it can never be the case, as asserted by Mayo, that a process such as that claimed by Prometheus can preempt the natural phenomenon or law of nature embodied in it.

V. ADOPTION OF THE RULE PROPOSED BY *AMICI* WOULD IMPROVE THE ADMINISTRATION OF THE PATENT LAW

As noted in our statement of interest, CONNECT and SDIPLA share the concern that the evolution of the law relating to the requirements that must be met by process claims to satisfy §101, although seemingly straightforward, has resulted in considerable confusion concerning its application to the extent that even patent professionals are not able to predict with confidence whether claims that embody so called fundamental principles are eligible for protection under the patent laws. If that position is in fact correct, then it can plainly be seen that the confusion necessarily discourages the formation of new companies or licensing efforts to exploit the technology. Any failure to exploit new technologies also necessarily means that new employment and new market opportunities and the resulting benefits to the public are lost to the economy.

We are certain that the Court is subjected to similar laments in many of the cases brought before it. However, we think there is actual empirical evidence supporting our concerns. Confirmation of these concerns can be found in a recent publication in the academic legal literature by respected professors of law who believe that the complexity of patent eligibility jurisprudence

surrounding §101 has become so great that post *Bilski*:

> "there is an enormous amount of speculation about the case's impact on patent applicants, litigants and other participants in the patent system. Most of the commentary is concerned with the holding in *Bilski*, how this holding will be applied by the courts and the Patent Office, and ultimately, the effect of the holding on inventors, and those who hold and seek patents."

See D. Crouch and R. Merges, *"Operating Efficiently Post-Bilski by Ordering Patent Doctrine* Decision-*Making*, 25 Berkeley Technology Law Journal 1674, 1675 (2010).

The situation is deemed so bleak by the authors that their proposed solution to the concerns of the stakeholders in the patent system would be to reorder the decision making steps conducted in prosecution and litigation of patent claims related to the requirements of patentability. Thus, instead of being the first or threshold inquiry[6], the determination of patent eligibility would actually become the last inquiry, so that patent eligibility under §101 is only considered in the situation where the claims are

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6 "The §101 patent-eligibility requirement is only a threshold inquiry." *Bilski*, 130 S. Ct. at 3225.

deemed to satisfy all other applicable requirements of Title 35.

We do not endorse this approach and are confident it will not prove influential in the prosecution and litigation of patent claims. The article, nevertheless, illustrates the difficulties faced by participants in the patent system in reaching informed decisions concerning the threshold requirement of patent eligibility. Instead of reordering the patentability decision tree, we think it preferable that any opportunity to clarify and simplify the determination of patent eligibility should be diligently pursued. It is in that spirit that CONNECT and SDIPLA urge this Court to not only affirm the decision of the Federal Circuit, but also adopt the rule that a process claim meeting the machine-or-transformation test be deemed to satisfy patent eligibility requirements.

VI. CONCLUSION

The ability to patent innovation is of such fundamental importance that our founders saw fit in the Constitution to specifically grant Congress power to establish a patent system. Their prescience has been borne out by history. There is likely no other time in history when the patent system has played such a vital role in inspiring innovation and encouraging investment in leading edge technologies. Therefore, it is vitally important that the legal framework for obtaining and enforcing patents not ossify, but instead

retain the maximum flexibility reasonably provided it by Congress to adapt to ever changing technology. A primary aim of the patent system should always be to foster, not hinder the development of new and unforeseen technologies.

It is, therefore, important that the Court use every opportunity to provide guidance to the lower courts, the Patent and Trademark Office, and the stakeholders in the patent system that simplifies the burden of determining whether innovation in emerging technologies will be protectable under the patent laws. That guidance is critical to informing whether a new discovery can even cross the threshold of §101 and enter the system Congress has established. Therefore, we encourage the Court to substantially improve the administration of §101 by adopting the rule that a process claim that meets the long, well established and easily understood machine-or-transformation test is not foreclosed from patentability by incorporating into the claim an application of a law of nature, natural phenomenon or abstract idea to the process.

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7 November 2011

AMICUS CURIAE BRIEF

RECORD AND BRIEF

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) *et al.*,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF GENOMIC HEALTH, INC., VERACYTE, INC., XDX, INC., BIODESIX, INC., TARGET DISCOVERY, INC., THE COALITION FOR 21ST MEDICINE, AND BAYBIO AS *AMICI CURIAE* IN SUPPORT OF RESPONDENT, PROMETHEUS LABORATORIES, INC.

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STATEMENT OF INTEREST[1]

This submission is made on behalf of the following entities ("Amici"), who are each active participants in the personalized medicine field.

Amici are vitally interested in the success of personalized medicine. As described below, each is involved at the forefront of this great, new frontier. Experience in the trenches has given Amici a unique perspective regarding the difficulties inherent in commercializing this emerging technology, and the recognition that patent protection is critically important to attract and retain private investment and drive future innovation. Accordingly, Amici respectfully request that the Court consider their views in resolving this case.

Genomic Health, Inc. is a personalized medicine company committed to improving the quality of cancer treatment decisions through the research, development and commercialization of genomic-based clinical laboratory services. To that end, the company conducts sophisticated genomic research to develop clinically-validated molecular diagnostics which provide individualized information on response to certain types of therapy, as well as the likelihood of disease recurrence. These diagnostic technologies generate information that healthcare providers and patients can use in making treatment decisions.

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[1] In accordance with Supreme Court Rule 37.6, *amicus curiae* states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than the *amicus curiae* or its counsel.

Veracyte, Inc. is a personalized medicine company pioneering the emerging field of molecular cytology. It is developing molecular tests designed to improve the diagnostic accuracy of cytology samples, thereby helping to increase the utility of these minimally invasive procedures as an alternative to surgical biopsy. Its solution permits diagnoses to be made without surgery by using small samples collected by minimally invasive techniques, and it uses a whole-genome approach to identify genes that best differentiate benignity and malignancy.

XDx, Inc. is a personalized medicine company that applies modern genomics technologies to the development of molecular diagnostic assays that translate a patient's immune status into clinically actionable information. The proprietary molecular expression technology used by XDx to develop testing for heart transplant patient management may be applicable to the post-transplant management of recipients of other organs.

Biodesix is a personalized medicine company focused on the development of diagnostic products that inform treatment decisions and improve patient care. The Company's goal is to give physicians more information about the patient and their disease; understanding the clinically meaningful information contained within each patient's molecular profile leads to better care and better outcomes. The Company's unique approach is based on ProTS(r), proprietary technology which exploits the power of mass spectrometry and enables the discovery of specific molecular profiles. Biodesix collaborates with clinical investigators to address critical clinical questions, and

partners with biotechnology and pharmaceutical companies to develop diagnostics to select patients most likely to benefit from novel therapies.

Target Discovery, Inc. is a personalized medicine company that discovers, validates, and utilizes protein isoforms to improve clinical diagnosis and management of disease. A growing body of scientific literature shows that protein isoforms correlate with disease state and patient-specific treatment. Most protein isoforms (90%) are made by the body after the protein is produced (post-translational modifications). Such protein modifications remain largely inaccessible to current immunodiagnostic and nucleic acid clinical assays. Target Discovery's products are designed to make this isoform biomarker information accessible to clinicians.

The Coalition for 21st Century Medicine is an organization in the personalized medicine field that represents more than two dozen of the world's most renowned diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists, and patient advocacy groups. The Coalition's core objective is to ensure that high quality, innovative diagnostic tests—necessary to assure that timely and accurate information is available when diagnosis, prognosis and therapy decisions need to be made—are available to patients and their physicians.

BayBio is Northern California's life science association that represents the region's 1,400 plus life science companies, including many innovators in the area of personalized medicine. It supports the regional bioscience community through advocacy, enterprise support, and enhancement of research collaboration. Its members include organizations engaged in, or

supportive of, research, development, and commercialization of life science technologies.[2]

SUMMARY OF ARGUMENT

For many years patents have been awarded for innovations in the personalized medicine area. The reliable issuance of such patents has been based on a solid legal foundation formed by this Court's precedent.

Key decisions of this Court wisely, and broadly, approved of patenting in the area of genetics as well as for concrete processes that use scientific principles at their heart. In *Diamond v. Chrakabarty*, 447 US 303, 314-16 (1980), this Court turned back a challenge to patents in the area of "genetic technology" as outside the scope of Section 101. This Court made clear that limits on patenting in cutting-edge technologies such as genetics is for Congress to decide unless they fall outside the very broad ambit of the statute. This Court's *Chakrabarty* opinion thus serves as a necessary reminder that extra-statutory exceptions to patent eligibility that have been judicially created are very narrow and should not place molecular diagnostic inventions at a disadvantage.

Reinforcing *Chakrabarty,* this Court explained in *Diamond v. Diehr* , 450 U.S. 175, 187 (1981) that the application of a scientific principle to a concrete and useful process constitutes patent-eligible subject matter.

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[2] In accordance with Supreme Court Rule 37.3(a), the parties to this litigation have consented to the filing of this brief by filing a blanket consent with the Court.

This Court explained that claims must be viewed as a whole and should not be "dissected" in constituent parts to determine what is new and what is not – only to find patent ineligibility based on a point of novelty. *Id.* at 193 n.15 ("The fact that one or more of the steps in respondents' process may not, in isolation, be novel or independently eligible for patent protection is irrelevant to the question of whether the claims as a whole recite subject matter eligible for patent protection under § 101.").

Moreover, as will be explained further below, the patent at issue in *Diehr* is similar in an important way to the type of medical diagnostic claims at issue in this case and which are important to Amici. Claim 11 in *Diehr* includes the step of "comparing" a measurement with a benchmark to "indicate" when to take action. This claim was specifically held patent-eligible by this Court even though it included mental steps of comparison and indication.

In light of this Court's decisions in *Chakrabarty* and *Diehr*, thousands of patents for innovations in the area of genetics and personalized medicine were sought and obtained over the last two decades. Reliant on the ability to patent their discoveries, private enterprise invested heavily in personalized medicine and freely disclosed invention-related data to the public.

The resulting patent-protected investments have created a nascent industry that, if allowed to continue to thrive, promises to dramatically reduce ballooning health care costs while improving lives. Further, led by American ingenuity and entrepreneurialism, this sector could serve as an economic engine for decades to come if

the fruits of investment are sheltered from copying through enforceable patent protection.

It bears emphasis that it is an expensive enterprise to create a medical test from the discovery of a relationship between a person's genetic make-up or disease biology and a better therapy. The "needle in a haystack" process of discovering the key relationship between a biomarker and the proper therapy is only the beginning. Beyond that: (1) costly and lengthy validation studies must prove to the satisfaction of skeptics the medical significance of the discovered relationship, (2) regulatory gauntlets must often be traversed by a cadre of high-priced professionals, and (3) entrenched interests in the medical field must be dislodged to make way for new tests that can eliminate traditional procedures that have long been profitable for the medical establishment. This process can take years, if not decades, and is filled with uncertainty at every turn.

Despite the mass expense and risk of creating a new diagnostic test from scratch, copying such a test can be remarkably easy. Once the relationship is proven, the validation data disclosed, the test approved, and the conventional wisdoms overcome, a new test can be simple and cheap to clone. The primary bulwark against such copying is enforceable patent protection.

Because the precious private sector investment described above is so dependent on reliable rules, it would be particularly unfair and destabilizing to invalidate the thousand of patents that have already issued, those in process, or those currently motivating ongoing or planned research and investment. But, more than that, it would be a devastating blow to the promise

of personalized medicine to compromise patent protection for this industry just as it is beginning to make a significant impact on patient care and helping to reduce the staggering cost of our health system. Amici thus respectfully request that the Court consider their views as it resolves this critical case. Their future is at stake.

ARGUMENT

I. THIS COURT'S PRECEDENT SUPPORTS THE PATENT ELIGIBILITY OF PERSONALIZED MEDICINE CLAIMS

A. This Court Has Upheld As Patentable Claims With The Step Of "Comparing" A Measurement With A Benchmark To "Indicate" When To Take Action

At the heart of personalized medicine is the recognition that biomarker tests can provide important information about how an individual should be treated medically.[3] Typically, patent claims covering such tests require the comparison of a biomarker with a benchmark that has been discovered. This comparison indicates a particular condition, severity of disease, or predicts a response to a specific therapy. Such a comparison and indication is often the heart of the innovation.

Respondent Prometheus, and the Federal Circuit, have done an effective job of explaining thoroughly why this Court's precedent supports the patent eligibility of claims covering such processes. There is no need for that to be repeated here.

But because Petitioner Mayo spends so much energy arguing that claims that include mental steps, thought comparisons, and perceived indications are dangerously improper, and because such claims can be a

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[3] For present purposes, a "biomarker" can be thought of as simply a biological characteristic of a person with meaning.

valuable tool to protect their inventions, Amici would like to direct the Court very specifically to Claim 11 from the *Diehr* case. There, this Court squarely held that Claim 11 was patent-eligible even though it includes the mental steps of (1) comparison and (2) recognizing an indication.

Claim 11 covers a process. The claimed innovation includes the use of the Arrhenius equation to determine how long to cure rubber. The claim requires a "comparison" between the elapsed time of the process with an optimized time for how long it should last: "*comparing* the resultant calculated total required cure time with the monitored elapsed time measured by said interval timer." In other words, you consider the required cure time and you compare that with the elapsed time shown on the timer. The claim also requires that when the comparison of the elapsed time and the calculated time are equal there is an "indication" of the need to open the machine: "opening said press when a said comparison of calculated total required cure time and monitored elapsed time *indicates equivalence*."

Claim 11 does not require the claimed comparison to be performed by a machine or require that the indication is appreciated by a machine. Rather, the claim plainly encompasses a comparison performed by the human mind and an indication appreciated by the human mind. Claim 11 is specifically set forth in full in the opinion at footnote 5. Thus, this Court's decision in *Diehr* itself confirms that claims that include within a specific process a comparison step and an indication step to be performed in the human mind are not somehow disqualified from patenting.

B. This Court Should Not Make Claim Drafting In Personalized Medicine Anymore Stilted, Arcane, Or Indirect Than It Needs To Be

Many inventions in the personalized medicine area arise from the discovery of a relationship between the genetic profile of a person and the optimized diagnosis and treatment of that person for a specific disease. This is frequently referred to in the briefing before the Court as a "correlation." There should be little doubt that it is inventive to identify and apply these correlations to a concrete process to improve the diagnosis and treatment of the unhealthy for a particular disease. It takes both inspiration and perspiration to create these inventions.

Mayo and supporting amici suggest that these kinds of diagnostic processes should be claimed, if at all, in a way that does not squarely focus on the bioinformation that is produced as part of the diagnostic test.[4] But the production of the bioinformation is often the heart of the innovation. It is illogical and unnecessarily complicating to create a requirement that such inventors claim their innovations indirectly by covering the method of detection of the biomarker or the ultimate therapy applied by a doctor, instead of allowing

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[4] Amici testing laboratories Arup and Labcorp argue that improvements in testing procedures should be patentable, but not the innovations at the core of the personalized medicine industry. Amicus Brief Of Arup Laboratories, Inc. and Labcorp In Support of Petitioner at 19 ("[T]he scope of patentable subject matter still may legitimately extend to innovative tests."). This is self-interested, but unsupported.

the inventor to cover the specific application of the correlation itself to generate a useful indication in a particular context. While such inventions may sometimes be claimed by reference to a new procedure for identifying a biomarker or to a consequent novel treatment, it should be encouraged in the right case to allow inventors to directly cover their innovation. This will often be the bioinformatic step of comparing the biomarker to a proven benchmark to create an indication for medical treatment. So long as that step is part of a concrete process with a particular application, there is no statutory or other bar to claim that innovation.

A contrary rule will make it more difficult to protect personalized medicine innovations, while also encouraging waste such as indirect claim drafting that merely attempts to surround the perimeter of the innovation. Patent claim drafting already suffers from too much emphasis on artfulness and formalisms. There is no good reason to exacerbate that problem in a field where, as explained above, patent protection is so important at this juncture in history.

II. THE PERSONALIZED MEDICINE INDUSTRY HAS EMERGED UNDER, AND THRIVED BECAUSE OF, ENFORCEABLE PATENT PROTECTION

A. Personalized Medicine Holds Great Promise, But Innovation and Ultimately Patient Care Will Suffer Without Patent Protection

Personalized medicine has the potential to revolutionize patient care by allowing physicians to design targeted treatments that both reduce the cost of healthcare and improve patient outcomes. Diagnostics for diabetes, cardiovascular disease, colorectal cancer, and breast cancer were demonstrated to save $899 million in avoidable healthcare costs in 2004.[5] Applying this life quality and financial savings across global populations and diseases, the power of this "disruptive technology" to improve healthcare is staggering.

As an example, XDx published a study which projected a savings of about $6,500 per heart transplant patient in five-year monitoring costs.[6] Similarly, a study by Genomic Health demonstrated that its breast cancer test saved the healthcare system about $2000 per patient by identifying patients who would likely not benefit from chemotherapy- expensive therapeutics with serious side effects that have on average only a 25% efficacy rate.[7]

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[5] This included avoidance of 56,200 adverse health events and up to 34,000 deaths. The Lewin Group, *The value of diagnostics innovation, adoption and diffusion into health care*, p. 2 (2005), citing National Committee for Quality Assurance, available online at http://www.socalbio.org/pdfs/thevalueofdiagnostics.pdf

[6] R. Evans, et al., The economic implications of noninvasive molecular testing for cardiac allograft rejection, Am J of Transplantation 5:1553-1558 (2005).

[7] J. Hornberger, et al., Economic analysis of targeting chemotherapy using a 21-gene RT-PCR assay in lymph node-negative, estrogen receptor-positive, early-stage breast cancer, Am Journal of Managed Care 11 (No. 5):313-324 (2005)

Even Mayo Clinic's President and CEO has acknowledged:

> The key to fixing America's broken healthcare system is to measure the value of healthcare instead of its cost...Individualized medicine, including biomarkers for tamoxifen and warfarin sensitivity and gene signature studies that are identifying other drug sensitivities in patients, can significantly improve the value we deliver to patients.[8]

In addition, many public health agencies have recognized the importance of supporting development of novel diagnostic tools, including FDA Commissioner Dr. Margaret Hamburg,[9] the President's Council of Advisors on Science and Technology,[10] the U.S. Department of Health & Human Services,[11] Patient-Centered

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[8] Personalized Medicine Coalition, The case for personalized medicine (2009), available at http://www.personalizedmedicinecoalition.org/sites/default/files/thecaseforpersonalizedmedicine

[9] FDA Office of the Chief Scientist, Advancing Regulatory Science, Section I (Oct. 2010), available online at http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScient/ucm228207.htm

[10] Office of Science and Technology Policy, Executive Office of the President, Priorities for Personalized Medicine (2008).

[11] Office of the Assistant Sec'y for Planning and Evaluation, U.S. Dept. of Health & Human Servs., Personalized Health Care: Pioneers, Partnerships, Progress (2008).

Outcomes Research Institute (created under the Patient Protection and Affordable Care Act),[12] and Congress.[13]

Diagnostics companies have invested based on the settled expectation that, if able to obtain clinical acceptance and payer reimbursement, novel tests would be protected from competitor copying for the remainder of their patent terms. As a result, in the United States personalized medicine has budded and blossomed into a $11.2 billion market that employed more than 40,000 people in 2005.[14]

B. Enforceable Patent Protection Is Critical To Investment In Personalized Medicine

The Congressional Research Service arm of the Library of Congress has documented that a key driver for research and development in medical technology is enforceable patent protection:[15]

> At the present time, the patent laws

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[12] The federal government allocated $1.1 billion in 2009 for Comparative Effectiveness Research to study the latest developments in molecular biology and to improve healthcare by taking into account the genetic makeup of patients.

[13] Genomics and Personalized Medicine Act of 2006, S. 3822, 109th Cong. (2006).

[14] Lewin Group, The Value of diagnostics innovation, adoption, and infusion into health care, p. 44 (2005).

[15] See, e.g., H. Grabowski, *Patents and New Development in the Pharmaceutical and Biotechnology Industries*, Fed. Res. Bank of Dallas, pp. 99-100 (2002), available online at http://fds.duke.ed/db/attachment/273

> provide a system under which all inventions are subject to the same requirements of patentability regardless of the technical field in which they arose. ...Innovators in biomedical industries tend to see patent protection as critically important as a way to prohibit competitors from appropriating the results of a company's research and development efforts.[16]

It is also recognized that the healthcare industry is an important part of the global economy, and that the industry relies upon intellectual property rights in order to compensate for large R&D, regulatory, clinical trial, and other costs.[17]

The patent system is essential to protect and drive biomedical innovation because it is the protection from copying for novel diagnostics that attract financial investment.[18] This is especially true for diagnostic tests, which like pharmaceuticals, are easily imitated.

Significantly, although running a commercial test may be relatively inexpensive, the process of biomarker

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[16] CRS Report for Congress, *Patent Reform: Issues in the Biomedical and Software Industries*, Order Code RL33367, CRS12-13 (Dec. 14, 2007).

[17] See, e.g., BIAC/OECD, Creativity, innovation and economic growth in the 21st Century: an affirmative case for intellectual property rights, p. 14 (Jan. 2004), available online at http://www.oecd.org/dataoecd/52/45/2335023.pdf

[18] C. Barfield, J. Calfee, Biotechnology and the Patent System, p. 4 (AEI Press, 2007).

discovery and assay development is quite costly. Novel diagnostic companies must invest millions of dollars to develop a test that ultimately may never be commercialized for a host of reasons. Much of the research costs are driven by the complexities of disease biology and the resulting need for huge amounts of patient tissues and data to generate sufficient statistical power to validate biomarkers, algorithms, and assays. Each sample of qualified patient tissue can cost hundreds or even thousands of dollars. In addition, the United States regulatory system currently lacks guidance about the level of evidence that is necessary for acceptance of novel diagnostics by payers, which has created inefficiencies in the development of and increased R&D costs. Compared to the late 1990s, diagnostic companies are now spending as much as three times more on R&D in the three years before product launch.[19] For example, in 2004 diagnostic companies invested approximately 35-200% of their revenue in R&D, as compared to 11-16% for medical device and pharmaceutical companies.[20]

A labyrinth of regulatory requirements also increases R&D costs. A 2011 study showed that the average total cost to obtain device clearance or approval from the FDA ranged from $31-$94 million, with of course no guarantees that a product will ever be marketed.[21] Clinicians have their own standards for

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[19] G. Gustavsen, et al., The Reimbursement Landscape for Novel Diagnostics, p. 15-16 (2010).

[20] Lewin Group, p. 56.

[21] MedIC Report, Vital Signs: The threat to Investment in U.S. medical innovation and the imperative of FDA reform (Oct. 2011).

demonstrating clinical utility and diagnostic predictability that must be demonstrated at the local level.

Perhaps most significantly, the adoption of new "game-changing" diagnostics threatens entrenched medical interests. Adoption of new products and tests face this additional source of systemic resistance. Personalized medicine reduces – and can eliminate altogether – the need for expensive, but reimbursable procedures that have long been staples of the healthcare economy. The revenues from these traditional procedures may be viewed as lifeblood for elements of the medical establishment and others who prosper from the *status quo*, including many of the amici supporting petitioner. This explains the medical establishment's concern about the disruptive changes to their business that will follow from a patent-incentivized personalized medicine industry.

Given the high costs of R&D, private funding is critical to the future of personalized medicine companies, many of whom have relatively limited resources with which to navigate the long and expensive research, development, and commercialization cycles required in this area.[22] Investors are keenly aware that patent exclusivity is absolutely necessary to have any hope of recouping the huge amount of investment necessary to launch a single successful product.

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[22] Testimony of M. Heesen (National Venture Capital Assoc.) at Joint Economic Committee Hearing, *Driving Innovation and Job Growth through the Life Sciences Industry*, pp. 5, 12-13 (May 25, 2011).

There is no basis to believe that academia, or the public sector, can nourish personalized medicine as effectively as can patent-protected private sector investment. Suggestions to the contrary by those against patents simply defy common sense.

III. SHIFTING RULES WOULD DESTABILIZE AND DISCOURAGE INVESTMENT IN NEW TECHNOLOGIES SUCH AS PERSONALIZED MEDICINE

This Court has long recognized the importance of a stable set of rules to encourage private sector investment. As demonstrated by a 2011 study of biomedical investment trends, any destabilization in the United States system of rewards used to promote diagnostics development will discourage investors and divert needed resources elsewhere.[23]

In *United States v. Title Insurance & Trust Co.*, 265 U.S. 472, 486-87 (1924) this Court stated that it has "long recognized the importance of stability and precedential consistency to protect investment-backed expectations in the law of real property."

As intellectual property has become increasingly central to the economy, this Court has emphasized the significance of stability for patent rights as least as emphatically as for real property. In *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 32, n.6 (1997), this Court explained the importance generally of

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[23] J. Makower, et al., *Vital Signs: The threat to investment in U.S. Medical innovation and the imperative of FDA reform* (Oct. 2011) ("MedIC Report").

preserving the policies and practices of the Patent Office in issuing patents: "To change so substantially the rules of the game now could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired and which would be affected by our decision."

Even more recently, in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002), this Court emphasized the importance of preserving the settled expectations of innovators, stating, "courts must be cautious before adopting changes that disrupt the settled expectations of the inventing community."

Over the last two decades, thousands of patents have issued in the area of personalized medicine. Specifically, the government has issued a large number of valuable biomarker patents covering a wide range of technologies, including innovative personal medical procedures. Georgetown's "DNA Patent Database" currently contains entries for over 60,000 granted U.S. patents, representing a 34% increase in granted patents in under five years.[24] A database of biomarkers contains over 30,000 unique sequences from patent

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[24] As of October 23, 2011, the database contains 60,365 U.S. patents and 94,433 patent applications. *DNA Patents Database*, (Nov. 2, 2011), http://dnapatents.georgetown.edu. This represents an increase of 34.2% over the 44,972 patents cited by Holman. Holman, Christopher M., *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, (Feb. 19, 2008), http://escholarship.org/uc/item/7rr0w5gf. ("As of August 24, 2007, the DNA patent database included 44,972 patents...").

applications.[25] Searches suggest many thousands of these patents have potential medical or diagnostic applications.[26] And a 2008 article noted that over 1,200 diseases could already be identified by genetic tests.[27]

Personalized medicine, like other revolutionary technologies before it, has not been easily accepted into clinical practice. It requires changes in regulation, reimbursement policies, and legislative protections for privacy. Consequently, the medical diagnostics industry remains in a delicate state due to challenges that have made it difficult to attract outside investment, even despite the cloud over patent protection.[28] As a result,

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[25] SciClips maintains a "diagnostic and prognostic biomarkers database" which contains over 30,000 entries that have been "reported in patent publications and PubMed abstracts." *Disease Diagnostic Biomarker Database*, (Nov. 2, 2011), http://www.sciclips.com/sciclips/diagnostics-biomarker-db.do.

[26] A November 2, 2011 search of the Google Patents database found that 8,050 patents contained *all* of the following words: "Diagnostic, testing, DNA, gene, nucleic acid," while a search for patents containing all of the terms "Medical, patient, treatment, cell, gene, sequence" found 5,300 patents. *Google Patents*, (Nov. 2, 2011) http://www.google.com/patents. Only 59 patents contain all of the terms from both searches, meaning that these two keyword clusters alone represent over 13,000 potentially relevant patents. *Id.*

[27] *Genetic Benefits at Risk*, Nature, 14 Feb. 2008, at 745-46. ("[I]n the five-and-a-half months since Nature last opined about this topic, the number of diseases for which genetic tests are available to patients has grown by 8.4%, to 1,236.").

[28] G. Gustavsen, et al., *The reimbursement landscape for novel diagnostics* (Jan. 2011), available online at http://www.bio.org/sites/default/files/Health_Advances&BIO_Novel_Diagnostics_Reimburs_20110103_0.pdf. The FDA and a bill drafted by Senator Hatch suggest that the clinical

17% of United States venture capital firms have decreased their investments in diagnostics companies over the past three years, and 21% expect to further curtail such investment in the future.[29]

Eliminating biomedical process patents, or creating uncertainty about their enforceability would likely cause a fatal crack in the industry's already-weakened foundation, setting back hopes for a new era of targeted and thus less expensive medicine.

IV. THE CREATION OF NEW EXCEPTIONS TO BROAD PATENT ELIGIBILITY IS FOR CONGRESS, NOT THIS COURT

Just last term in *Bilski v. Kappos*, 130 S.Ct. 3218, 3225 (2010) this Court again acknowledged that "Congress plainly contemplated that the patent laws would be given wide scope," citing *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980). This Court also acknowledged that *stare decisis*, not the governing statute itself, is the identified authority for the existing judge-made exceptions.[30] *Id.* at 3225 ("[T]hese

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validity of diagnostic tests will soon undergo new regulatory scrutiny.

[29] J. Makower, et al., Vital Signs: The threat to investment in U.S. Medical innovation and the imperative of FDA reform, p. 100 (Oct. 2011).

[30] Chief Judge Rader of the Federal Circuit aptly referred to the judge-made exceptions to Section 101 as the "substantive due process" of patent law because of the lack of textual support for them in law, while highlighting the dangers of this mode of analysis. *Classen Immunotherapies, Inc. v. Biogen IDEC*, __ F.3d

exceptions are not required by the statutory text."). For this reason alone, the exceptions should remain narrow and should not be expanded based on the policy preferences of Mayo and its amici.

Indeed, this Court has long redirected the question of exceptions to patent eligibility to Congress. In *Chakrabarty*, this Court rebuffed a frontal assault on patenting in the area of genetics. The Court rejected that assault, explaining that it was not for the Court to create new exceptions to Section 101:

> The choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot. That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives. Whatever their validity, the contentions now pressed on us should be addressed to the political branches of the Government, the Congress and the Executive, and not to the courts.

__ (Fed. Cir. 2011) (Rader, C.J., additional views) ("Subject matter eligibility under section 101 has become the 'substantive due process' of patent law — except that reading non-procedural requirements into the constitutional word 'process' has more historical and contextual support than reading abstractness into the statutory word 'process' because Title 35 already contains ample protections against vague claims. *See* 35 U.S.C. § 112.").

In essence, Mayo has asked this Court to reformulate Section 101 to outlaw enforceable medical diagnostic claims. But this is an issue for Congress, just as it was in *Chakrabarty* when remarkably similar policy arguments were tendered. Congress regularly considers legislation from those who oppose patenting in this area, and can address any such concerns using more nuanced solutions than a court deciding a single case on its own idiosyncratic facts.

Indeed, in the recently passed America Invents Act, Congress accepted a specific limitation on patenting in life sciences, enacting an anti-cloning provision that "no patent may issue on a claim directed to or encompassing a human organism." *Id.* § 33(a). Likewise, Congress has amended the patent law to ban infringement claims involving "medical activity" performed by "medical practitioners." *See* 35 U.S.C. § 287(c).

Although some limited attempts to narrow patenting in life sciences have been successful, many more aggressive attempts, such as that presented by Mayo in this Court, have been rejected by Congress. Notably, in 2007, Representative Xavier Becerra introduced the Genomic Research and Accessibility Act (GRAA), which would have prospectively barred the patenting of any "nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies."[31] The House Committee on the Judiciary, Subcommittee on the Court, the Internet, and Intellectual Property held a hearing related to that bill entitled "Stifling or Stimulating—The Role of Gene

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[31] H.R. 977, 110th Congress, 1st Session (Feb. 9, 2007).

Patents in Research and Genetic Testing."[32] Four witnesses presented testimony. Not one of the witnesses testified in support of the GRAA or advocated any sort of legislation limiting the patentability of gene testing. The bill received little support and was not passed.

In 2002, Representative Lynn Rivers introduced the Genomic Research and Diagnostic Accessibility Act.[33] That bill would have provided limited liability exemptions for certain uses of patented genetic sequence information in the context of basic research and genetic diagnostic testing, but would not have affected the patentability of genetic inventions. The bill received little support and also did not pass.

Collectively, this legislative history reflects Congress' understanding that gene sequence and process patents are properly within the scope of Section 101. Where narrow limitations have been deemed appropriate, they have been enacted – including as recently as two months ago. Amici respectfully request that the Court take notice of this legislative record and defer to Congress on the policy issue of whether diagnostic correlation patents should, for some reason, be excluded from what is patentable.

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[32] *See* http://judiciary.house.gov/oversight.aspx?ID=390.

[33] H.R. 3967, 107th Congress, 2nd Session (Mar. 14, 2002).

CONCLUSION

For the foregoing reasons, this Court should affirm the decision of the Federal Circuit.

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

NOV - 1 2011

No. 10-1150

IN THE
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF HEALTH LAW, POLICY, AND ETHICS SCHOLARS AS AMICI CURIAE IN SUPPORT OF RESPONDENTS

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QUESTION PRESENTED

Whether a process for determining safe and effective dosages of prescription medicines based on the unique chemistry of individual patients contains patentable subject matter under 35 U.S.C. § 101.

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INTERESTS OF *AMICI*[1]

Amici are scholars of health law, policy, and ethics.[2] They have devoted their careers to the study and promotion of public health. Their perspective reflects a broad utilitarianism that seeks the greatest good for the greatest number. Public health focuses on populations rather than individuals, and collective goods rather than personal rights or interests. The foundational public health principle affirms one simple objective: to prevent avoidable suffering and death. *See Public Health Law and Ethics* xxiii (Lawrence O. Gostin, Univ. of Cal. Press 2002.

Amici have concluded that patent eligibility for claims to medical diagnostic and treatment processes prevents avoidable suffering and death. Steady improvement in medical treatment methods, especially for complicated, risky, and painful therapies, is vital. Advancement at some short-term cost is better than no advancement. The removal of long-standing incentives to improve disease treatment could do enormous damage to medical progress. This Court should not limit the arsenal of incentives available to combat future health threats.

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[1] The parties have lodged blanket letters of consent to the filing of amicus briefs with the Clerk of the Court. No counsel for a party authored this brief in whole or in part, and no person other than *amici* or their counsel made a monetary contribution to its preparation or submission.

[2] A complete list of *amici curiae* is set forth in the Appendix to this brief. The views presented here do not reflect those of any institution or organization.

Amici respectfully disagree with the ethical position set out in the brief of the American College of Medical Genetics, *et al.* ("Medical Associations' Br."). That brief highlights an opinion by the American Medical Association ("AMA") that patents on medical procedures are "unethical." It advocates a more restrictive patent policy that would deny protection for all innovative diagnostic and treatment methods. But that position undervalues the long-term costs of excluding innovative medical procedures from the patent system. *Amici* are sympathetic to some of the practical concerns raised by the medical associations. But Congress and the Executive are better positioned than this Court to resolve those concerns.

SUMMARY OF ARGUMENT

The physician inventors in this case identified a serious medical problem affecting millions of people, dedicated themselves to solving it, and succeeded. Autoimmune diseases, like Lupus, Crohn's disease, Graves' disease, or Type I Diabetes, turn the human body against itself. Instead of protecting healthy cells, tissues, and organs from foreign pathogens, diseased immune systems attack and destroy them. The appropriate therapeutic response is to suppress the patient's confused immune system. But disabling a body's natural defenses just enough to quiet the mutiny and not cause further harm is complicated and extremely risky. For years, the standard treatment method was trial and error: prescribe conservatively, then "wait and see." The patents-in-suit make claims to a better treatment process—a way of quickly pinpointing the effective

dosage for a particular patient. The question for this Court is whether that improvement—and other diagnostic and treatment processes like it—falls within the scope of patentable subject matter under 35 U.S.C. § 101.

Amici write to advocate caution in the Court's resolution of this question and offer Hippocrates' own counsel: First, do no harm. Patent protection for medical process inventions has resulted in long-term benefits to public health, benefits that result from both private investment, and increased public knowledge. This Court should not limit the arsenal of incentives available to combat future health threats. The "ethical" objections raised by the medical associations reflect a misplaced emphasis on the short-term concerns of individual patients at the expense of long-term public welfare.

ARGUMENT

I. MEDICAL PROCESS PATENTS ADVANCE PUBLIC HEALTH

A long-term, population-based approach to patent policy offers compelling reasons to maintain the patentability of medical diagnostic and treatment processes: those inventions save lives over time. Their patentability encourages sensible private investment in medical advances and fosters widespread public dissemination of medical discoveries.

A. Section 101 Authorizes Medical Process Patents

The Founders enshrined in the Constitution their empirical judgment that patents promote societal progress. Article I, Section 8, of the U.S. Constitution provides Congress with the power "To promote the Progress of Science" "by securing for limited Times to" "Inventors the exclusive Right to their" "Discoveries." Accordingly, Congress enacted Section 101, which describes what is patentable: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent thereof, subject to the conditions and requirements of this title." 35 U.S.C. § 101. By providing a "limited Time[]" in which an inventor can exclude others from an invention, the patent laws promote "Progress."

In drafting Section 101 of the Patent Act, Congress "plainly contemplated that the patent laws would be given wide scope," *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980), and chose "extremely broad" language in describing patent eligibility, *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Intern., Inc.*, 534 U.S. 124, 130 (2001). It enacted "a dynamic provision designed to encompass new and unforeseen inventions," *id.* at 135; *see also Chakrabarty* at 316. And, at each opportunity, Congress has maintained its expansive view of patentable subject matter, to the benefit of American progress. *Classen Immunotherapies, Inc. v. Biogen, IDEC*, 2011 WL 3835409 at *17 (Fed. Cir. Aug. 31, 2011) (additional views of Rader, C.J., and Newman,

J.) (affirming patent eligibility for medical methods and comparing the stifling effects of eligibility restrictions in Europe with the benefits of strong American patent protection).

Accordingly, this Court has explained that "ingenuity should receive a liberal encouragement," *Chakrabarty* at 308 (quoting 5 *Writings of Thomas Jefferson* 75-76 (H. Washington ed. 1871)), to "fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts' with all that means for the social and economic benefits envisioned by Jefferson," *id.* 315. It "has more than once cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed." *Diamond v. Diehr*, 450 U.S. 175, 182 (1981) (citations and internal quotation marks omitted).[3]

Consistent with the contemplated breadth of patentable subject matter, Section 101 does not exclude medical process patents. As the Solicitor General notes, "patent laws have long been understood to encompass improved methods of

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[3] Congress's forward-looking commitment to the benefits of the patent system undermines this Court's now-outdated caution in *Flook* to avoid the extension of patent rights into areas "wholly unforeseen by Congress," *Parker v. Flook*, 437 U.S. 584, 596 (1978). *Flook* relied on a narrow statutory reading in *Deepsouth Packing Co. v. Laitram Corp.*, 406 U.S. 518, 531 (1972), which Congress subsequently overturned. *See* 35 U.S.C. § 271(f); *Microsoft Corp. v. AT&T Corp.*, 550 U.S. 437, 443-44 (2007); Pub. L. No. 98-622, Title I, § 101(a), 98 Stat. 3383 (Nov. 8, 1984). That Congressional "correction" demonstrates that the scope of patentable subject matter is broad to encourage and reward "wholly unforeseen" innovation.

treating patients to alleviate medical disorders." U.S. Br. 9. Indeed, for over 100 years, Congress has declined invitations to exclude medical treatment methods from Section 101. *See* H.R. 12451, 57th Cong. (1902); H.R. 1127, 104th Cong. (1995); *see also* Joel J. Garris, *The Case for Patenting Medical Procedures*, 22 AM. J.L. & MED. 85, 107-08. And for more than 50 years, the U.S. Patent and Trademark Office Board of Appeals has held that medical methods are patentable. *Ex parte Scherer*, 103 USPQ 107 (1954).

So too, the American Medical Association has explained that Section 101 covers medical processes. In describing this Court's opinion in *Chakrabarty*, the AMA's Council on Ethical and Judicial Affairs acknowledges that the "decision to broadly interpret the statutory scope of patentable inventions [under 32 U.S.C. § 101] makes it highly unlikely that medical procedures can be legally excluded from the legal definition of process without additional legislative action." AMA, *Report of the Council on Ethical and Judicial Affairs, Ethical Issues in the Patenting of Medical Procedures* 1 (1995) ("AMA 1995 Report").[4] A 2007 follow-up report likewise concedes that "U.S. patent law allows for the patenting of medical procedures." AMA, *Report of the Council on Ethical and Judicial Affairs, Amendment to Opinion E-9.095, Trademarks,*

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[4] Available at http://www.ama-assn.org/resources/doc/ethics/ceja_1a95.pdf.

Patents, Copyrights, and Other Legal Restrictions on Medical Procedures 2 (2007) ("AMA 2007 Report").[5]

The AMA's legislative efforts also confirm that Section 101 covers medical process patents. The AMA lobbied Congress to exclude medical procedure patents from the Patent Act's protection. *See* H. R. 587, 104th Cong., 1st Sess. (1995). Congress rejected medical lobbyists' initial attempts to restrict patentable subject matter, Weldon E. Havins, *Immunizing the Medical Practitioner "Process" Infringer: Greasing the Squeaky Wheel, Good Public Policy, or What?*, 77 U. DET. MERCY L. REV. 51, 63-64 (1999) (noting that the original proposal for § 287(c) attempted to prohibit patents on "any invention or discovery of a technique, method, or process for performing a surgical or medical procedure, administering a surgical or medical therapy, or making a medical diagnosis"). It then created Section 287(c)(1) to grant immunity from patent infringement suits to both "'medical practitioners' and 'related health care entities': when they engage in protected 'medical activity.'" 35 U.S.C. § 287(c)(1). Fears of the medical community were dominant factors shaping the content and scope of § 287(c). Jeff S. Rundle, *The Physician's Immunity Statute: A Botched Operation or a Model Procedure?*, 34 J. CORP. LAW 944, 948 (2009). The very premise of the AMA's efforts that resulted in Section 287(c)(1) is that Section 101 permits medical process.

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[5] Available at http://www.ama-assn.org/resources/doc/code-medical-ethics/9095b.pdf.

B. Medical Process Patents Encourage Private Investment

Patent law protects medical diagnostic and treatment innovations for the same reason it protects all types of inventions: patents spur progress.

Innovation in disease treatment is complicated and expensive. At the frontiers of medical science, the balance between risk and reward weighs heavily against making any effort. Research and development merely initiate the costly process of bringing an effective therapeutic intervention to market. Production, clinical trials, regulatory compliance, distribution, monitoring and insurance for adverse outcomes, and physician education all draw on limited investment resources.

Moreover, the growing imperative to contain health care costs makes "competitiveness and economic advantage...increasingly important." Todd Martin, *Patentability of Methods of Medical Treatment: A Comparative Study*, 82 J. PAT. & TRADEMARK OFF. SOC'Y 381, 384 (2000). Almost any flavor of health care reform will rely on managed care. As available capital decreases, both public and private investors will be less likely to risk considerable spending on research that may not produce any value.

In this economically constrained environment, patents preserve the financial feasibility of investments in medical research. Private investors allocate resources based on whether the end result

can be commercialized and patented, not whether medical technology will be advanced. Innovative medical methods are cheaply reproduced by others, and without some promise of exclusivity, investment fades. Su-hua Lee, *Patent Protection for Essential Biomedical Inventions and Its Impacts on the Implementation of Public Health*, 5 ASIAN J. WTO & INT'L HEALTH L. & POL'Y 115, 117 (2010) ("Without patents...better medical products needed to overcome...diseases would not be developed."). Patents motivate innovators with the promise of financial reward. Robert P. Merges, *Uncertainty and the Standard of Patentability*, 7 HIGH TECH L.J. 1, 2 (1992) (concluding that one function of the Patent Act is to encourage research with an uncertain prospect of success at its outset); *see also, Eldred v. Ashcroft*, 537 U.S. 186, 247-48 (2003).

Additional factors align medical process patents with the public interest. Patents on diagnostic tests provide incentives for scientist-inventors to innovate beyond the basic, government-funded research for which no patent can be sought, and *apply* that theoretical research to a useful product.[6] That

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[6] A basic research discovery cannot be patented unless the inventor can credibly describe the discovery's "specific and substantial" utility. U.S. Patent and Trademark Office, "2107 Guidelines for Examination of Applications for Compliance with the Utility Requirement." Available at www.uspto.gov/web/offices/pac/mpep/documents/100_2107.htm. *See also Brenner v. Manson*, 383 U.S. 519, 534 (1966) (A process claim must be reduced to a specific product, lest it "engross a vast, unknown, and perhaps unknowable area...[and] block off whole areas of scientific development without compensating benefit to the public.")

useful product is the benefit upon which the patent *quid pro quo* is based. *Brenner v. Manson*, 383 U.S. 519, 534 (1966). Basic research underpins, for example, the pharmaceutical industry's search for new drugs, but does not replace or duplicate it. *See, e.g.*, Congressional Budget Office, *Research and Development in the Pharmaceutical Industry*, 3 (2006) ("CBO Report") ("[P]rivate firms focus much more on applied research and development.").[7]

Additionally, medical process patents appropriately align investment incentives to expected consumer value: The patentee's profits as a monopolist are tied to demand. If an innovation is of no use to people, the innovation will not lead to private investment. But a patentable innovation that is of considerable use to sick people, for example, will likely produce a return and justify appropriate capital investment in research.

The human fertilization technology developed in the 1980s illustrates how process patents promote medical progress. *See, e.g.*, Martin at 384; Steven L. Nichols, *Hippocrates, the Patent-Holder: The Unenforceability of Medical Procedure Patents*, 5 GEO. MASON L. REV. 227, 258 (1997). Surrogate embryo transfer technology transfers an embryo from one woman to another. The technology was financed by private investment funds after the National Institutes of Health declined to fund the project. William D. Noonan, *Patenting Medical and Surgical Procedures*, 77 J. PAT. & TRADEMARK OFF.

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[7] Available at http://www.cbo.gov/ftpdocs/76xx/doc7615/10-02-DrugR-D.pdf.

SOC'Y 651, 656-57 (1995). Without the promise of patent protection, the technology would not have been developed.

Today's wealth of new medical diagnostics and treatments confirms that the patent system currently promotes the public interest. According to the Congressional Budget Office, "[t]he range of illnesses for which drug therapies exist has never been broader, and technological advances have yielded new drug treatments of increasing sophistication, convenience, and effectiveness." CBO Report at 4. The existing broad protection for medical process patents contributes substantially to these successes. *See* Garris at 93.

C. Medical Process Patents Increase Public Knowledge

Medical patents encourage widespread and immediate dissemination of medical knowledge. That is their entire purpose—patents offer the potential for limited financial rewards ex ante, but in exchange, they require full disclosure ex post. They are contracts "made by the acceptance...of the offer...to *disclose* [an] invention, in consideration that the United States will secure...the exclusive use and sale of it for [20] years." *Century Elec. Co. v. Westinghouse Elec. & Mfg.*, 191 F. 350, 354 (8th Cir. 1911).

To be sure, the medical community exchanges important information through publication in professional journals. Garris at 93. Publication offers professional recognition, which further

incentivizes research. And because patents limit the free use of inventive research, some fear that "[p]atenting medical processes...may adversely affect the development of new medical knowledge by limiting the willingness of researchers to share their work or to report its results in an objective manner." Gregory F. Burch, Note, *Ethical Considerations in the Patenting of Medical Processes*, 65 TEX. L. REV. 1139, 1139 (1987).

But patents do not disrupt professional norms of disclosure. Cynthia M. Ho, *Patents, Patients, and Public Policy: An Incomplete Intersection at 35 U.S.C. § 287(c)*, 33 U.C. DAVIS L. REV. 601, 625 (2000). To the contrary, an inventor can publish her innovation immediately in any accommodating publication and subsequently apply for a patent within a year of the invention's initial disclosure. 35 U.S.C. § 102(b) (setting forth the "public use" or "on-sale bar," which states that a patent may not issue if "the invention was...described in a printed publication...or in public use or on sale in this country, more than one year prior to the date of the application...."). Furthermore, the international academic culture of patenting does not differ significantly from the established culture of publishing scholarship. *See Chou v. Univ. of Chi.*, 254 F.3d 1347, 1359 (Fed. Cir. 2001) ("[B]eing considered an inventor of important subject matter is a mark of success in one's field, comparable to being an author of an important scientific paper."). Both accomplishments are regularly taken into account in recognizing academic achievement.

In fact, the patent system may *better* facilitate dissemination of medical knowledge than publication in professional journals. Under U.S. patent law, the inventor must not only disclose the invention, but explain it in such full, clear, and succinct terms as to enable any person skilled in the art to replicate it. 35 U.S.C. § 112. Medical journals have no such requirement. Nor do they publish all data submitted to them—the peer review process necessarily narrows the spectrum of publishable research. Martin at 385. *See also* Brian McCormick, *Just Reward or Just Plain Wrong? Specter of Royalties From Method Patents Stirs Debate*, 37 AM. MED. NEWS, Sept. 5, 1994 at 3 (describing Dr. John Stephens' unsuccessful efforts to publish the use of ultrasound to determine gender in utero before securing a patent for that use); Allan Bloomberg, *et al.*, *Patenting Medical Technology: "To Promote the Progress of Science and Useful Arts,"* 317 NEW ENG. J. MED. 565, 567 (1987) (describing the failure of publication to make an improved catheter used to diagnose heart disease widely available until it was patented).[8]

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[8] For example, after a leading professional journal summarily rejected Dr. Samuel Pallin's description of his "stitchless" method for cataract surgery, he sought a patent. Joseph Reisman, *Physicians and Surgeons as Inventors: Reconciling Medical Process Patents and Medical Ethics*, 10 HIGH TECH L. J. 355, 366 (1995) (citing Congressional testimony of Dr. Samuel L. Pallin that "I was denied the opportunity to publish my writings and discovery in a traditional medical journal. I turned to the U.S. Patent Office to document what I had accomplished...."). The Office granted Pallin's patent, and the procedure became—and remains—standard medical practice.

Moreover, while a subscription to one medical journal alone is expensive and access to all medical journals prohibitive for most, every patent document issued in the United States is in the public domain. The contents of the entire USPTO database—roughly 8 million patents and 3 million applications—are readily available online via the Office's Web site (or the slightly more user-friendly www.google.com/patents). Even bulk patent downloads are available to the public free of charge.[9] And patent documents can be made available immediately, whereas medical journals often suffer from delays associated with the submission, review, and publication process.

The alternative to patent protection for those seeking a reasonable return on their investment is often a far worse option for the spread of medical knowledge: total secrecy. Inventors who are denied the benefits of the Patent Act may choose to keep their inventions to themselves to prevent others from copying their work. Particularly as managed health care and the nationalization of insurance norms impose greater financial pressures on the health care system, those denied patent eligibility may seek trade secret protection to enable their continued research. *See* Garris at 92 & n.83.

The primary difference between a patent and a trade secret is that the public disclosure of a trade secret is legally *prohibited*—it destroys protection; whereas the public disclosure of a patent is legally

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[9] *See* http://www.google.com/googlebooks/uspto-patents.html.

required—it enables protection. Additionally, the force of a patent is limited to a certain period of time; the innovation ultimately returns to the public domain once the patent expires. But a trade secret lasts as long as there is a protected secret. *See* Kara W. Swanson, *Food and Drug Law as Intellectual Property Law: Historical Reflections*, 2011 WIS. L. REV. 331, 367 (2011) ("Patents are often understood as a complementary choice to trade secrets, offering a strong limited-term monopoly in exchange for public disclosure.").

Trade secrecy not only arrests dissemination of medical knowledge, it also puts patients' safety at risk. When novel technologies are kept secret, the medical profession has no opportunity to review whether those potentially innovative techniques are safe and effective.[10]

As a logical middle ground between unprotected public disclosure and secrecy, medical patents are often the best way to expand public knowledge.

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[10] The favorite historical example of this effect is the obstetrical forceps, which the Chamberlen family kept a secret through four generations of physicians. Andres Rueda, *Cataract Surgery, Male Impotence, Rubber Dentures and a Murder Case—What's So Special About Medical Process Patents?*, 9 U. BALT. INTELL. PROP. L.J. 109, 132 (2001).

II. THE ETHICAL CONCERNS RAISED BY THE MEDICAL ASSOCIATIONS ARE SHORTSIGHTED OR MISDIRECTED

The Medical Associations' Brief raises ethical arguments to justify the legal exclusion of diagnostic and treatment methods from patentable subject matter. The brief (at 16-17) highlights Opinion 9.095 of the AMA's Code of Medical Ethics, which states that the "use of patents...to limit the availability of medical procedures places significant limitation on the dissemination of medical knowledge, and is therefore unethical."

The AMA's position overemphasizes the immediate concerns of individual patients to the detriment of long-term public health. Although the medical associations raise legitimate practical concerns about the consequences of patent protection for medical processes, these concerns are for Congress or the Executive rather than this Court to address.

A. The Medical Associations' Objection To Medical Process Patents Reflects A Shortsighted Focus On Individual Patients

Medical ethics focuses on the individual patient even at the expense of long-term public welfare. The AMA's objection to medical process patents illustrates this tendency to prioritize the immediate needs of individual patients over what is best for society in the longer term.

i. Contemporary medical ethics advances the interests of individual patients

Modern medical ethics is focused on the individual. It was born in the wake of forced experimentation by Nazi scientists during the Second World War and found its first expression in the post-war Code of Nuremberg. Ian Kennedy and Andrew Grubb, *Medical Law*: Text with Materials 1011-26 (Butterworths 2d ed. 1994). In an effort to prevent the future dehumanization of patient-subjects, the Nuremberg Code outlined a set of clinical norms built around individual patient autonomy. Onora O'Neill, *Autonomy and Trust in Bioethics* 19-20 (Cambridge University Press 2002).

Today's medical ethics flourishes within that historical context; it focuses heavily on the personal interests and rights of individual patients. Its central concerns remain the protection of individual patient autonomy against the self-interest of the physician. Deirdre Dwyare, *Beyond Autonomy: The Role of Dignity in "Biolaw,"* 23 OXFORD J. LEGAL STUD. 319, 328 (2003). The predominant bioethics text, Tom Beauchamp and James Childress' *Principles of Biomedical Ethics*, prioritizes the individual patient's rights and well-being as the post-Nazi era watch cry of medical practice. *See* Marc A. Rodwin, *Strains in the Fiduciary Metaphor: Divided Physician Loyalties and Obligation in a Changing Health Care System*, 21 AM. J.L. & MED. 241, 247 (1995). That individual patient-centered paradigm has richly informed the practice of modern medicine for the better. It raised physicians'

awareness of their duties to individual patients and to potential conflicts of interest.

Consistent with this focus on the individual patient, the American Medical Association's Code of Medical Ethics ("AMA Code") prioritizes responsibility to the patient over general public obligations. The Code first states that "[a] physician shall recognize a responsibility to participate in activities contributing to the improvement of the community and the betterment of public health," AMA Code, xiv, ¶ VII (2001). But it quickly clarifies that "a physician shall, while caring for a patient, regard *responsibility to the patient as paramount*," *id.* at xiv, ¶ VIII (emphasis added), and that the fundamental doctor-patient relationship obligates a physician to "place patients' welfare...above obligations to other groups." *Id.* § 10.015. *See also* Douglas Mossman, *Critique of Pure Risk Assessment or Kant Meets Tarasoff*, 75 U. CIN. L. REV. 523, 578 (2006) ("In traditional medical ethics, doctors serve individual patients and have fiduciary obligations to them, not those around them.").[11]

A physician's commendable sensitivity to an individual patient's immediate welfare can distort

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[11] The AMA's focus on the individual patient also arose out of concern that physicians not sacrifice health for profit. *See, e.g.*, Stephanie P. Browner, *Profound Science and Elegant Literature: Imagining Doctors in Nineteenth-Century America*, 15-38 (Univ. of Penn. Press 2005) (discussing enduring conceptualizations of medical science as distinct from the selfish pursuit of pure profit); Kara W. Swanson, *Food and Drug Law as Intellectual Property Law: Historical Reflections*, 2011 WIS. L. REV. 331, 368-69 (2011).

her perspective on long-term policymaking. *See, e.g.*, William M. Sage, *Relational Duties, Regulatory Duties, and the Widening Gap Between Individual Health Law and Collective Health Policy*, 96 GEO. L.J. 497, 499-501 (2008). Physicians and their professional associations may value individual autonomy and patient-specific protections from potential conflicts of interest more than the general health and well-being of the community. Gostin at 67. They may also attend more closely to a given policy's effect on one particular patient than to its lasting effects on future patient groups. *See, e.g.*, Richard Saver, *In Tepid Defense of Population Health: Physicians and Antibiotic Resistance*, 34 AM. J.L. & MED. 431, 484 (2003) (linking the long-term problem of antibiotic resistance to the individual-patient paradigm in medical practice). The defining values of medical ethics are thus "sometimes...harmful to critical thinking about healthy communities." Gostin at xxiii.

ii. The medical associations' objection to medical process patents serves the interests of individual patients at the expense of long-term public welfare

Consistent with the AMA's principles of prioritizing the individual over the public, the AMA has long grounded its opposition to medical process patents in concern for the individual patient under the care of the health professional. The original version of its opinion opposing medical process patents complained that patents "pose substantial risk to the effective practice of medicine by limiting the availability of new procedures to patients and

should be condemned on this basis." AMA 1995 Report at 8.

The opinion's accompanying report expanded on the AMA's focus on the individual: "One of the fundamental principles in medicine is that the health of the patient is a physician's most basic concern." *Id.* at 3. The first and primary reason that the report opposed medical process patents was "the unacceptable picture of a patent procedure becoming unavailable to patients who require it." *Id.*

The AMA's admirable fidelity to the individual patient's rights and needs has misled it in this instance to a counterproductive position on patent policy. In some cases a particular patient may not benefit immediately from a new innovation because the patent puts the new improvement out of his financial reach. Over time, however, the investment and knowledge made possible by patent protection leads to improved public health. By failing to balance this side of the patent equation, the medical associations' orientation towards medical process patents in this case demonstrates how medical ethics are "sometimes...harmful to critical thinking about healthy communities." Gostin at xxiii.

In 2007, the AMA revisited, and shifted, the rationale for its opposition to medical process patents. The AMA deleted reference to the effective practice of medicine. Instead, the AMA revised Opinion 9.095 "to further emphasize the policy's emphasis on sharing medical knowledge." AMA 2007 Report at 4. The AMA also addressed trade secret protection and confidentiality agreements.

The AMA's Code now emphasizes the "significant limitation on the dissemination of medical knowledge" patents may cause. AMA Code of Medical Ethics, Opinion 9.095.[12]

As with its focus on the individual patient, the AMA's attachment to traditional modes of sharing medical knowledge minimizes the long-term value to the public welfare that patent protection affords. The AMA's revised view also reflects its earlier assertion that medical process patents do not promote progress.[13] That view conflicts with the Founders' empirical judgment, embedded in the Constitution, that patents do promote societal progress.

Indeed, for other types of patents the medical associations recognize the contributions to patient health and welfare made possible by innovations protected under the Patent Act. The associations write that the "patent system has served patients and the medical profession well, drawing investment into the development of new treatments."). Medical Associations' Br. 10-11. The associations also agree that "health-care-related patents can enhance the

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[12] Available at http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion9095.page.

[13] In its 1995 report, the AMA writes: "While the argument that the patenting of medical processes is necessary to enable and promote procedural advances seems strong initially, there is no evidence of the argument's empirical soundness." AMA Council on Ethical and Judicial Affairs, Report 1 – A-95, "Ethical Issues in the Patenting of Medical Procedures" at 6 (1995) ("1995 AMA Report"). http://www.ama-assn.org/resources/doc/ethics/ceja_1a95.pdf.

provision of high-quality...medical care." *Id.* at 10. And the AMA's Code of Medical Ethics, Opinion 9.09 explicitly permits physicians to patent a surgical or diagnostic instrument, conceding that "[t]he laws governing patents are based on the sound doctrine that one is entitled to protect one's discovery."[14]

The medical associations provide no reason why the "sound doctrine that one is entitled to protect one's discovery" should not also apply to medical process patents. As explained above, medical process patents promote patient health and welfare. From a medical perspective, the relevant question should be whether the invention promotes public health. The medical associations provide no reason to distinguish among different *kinds* of medical innovations amenable to patent protection.

B. The Medical Associations' Practical Concerns Should Be Directed To The Executive Or Congress

The AMA report that informed Opinion 9.095 also raises practical objections to medical process patents based on how the Patent and Trademark Office ("PTO") interprets provisions of patent law other than Section 101. These and similar real-world concerns have considerable force. But just as

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[14] *Cf.* F. E. Stewart, *"Is It Ethical for Medical Men to Patent Medical Inventions?"* 29 JAMA 583-87 (1897) ("The only object in patenting a medical invention is to utilize it for money-making purposes.... The medical inventor...will unconsciously use his best endeavor to promote the sale of his goods, rather than make it his chief object to benefit his patients who may purchase his goods.").

in *Chakrabarty*, the "contentions now pressed on [the Court] should be addressed to the political branches of the Government, the Congress and the Executive, and not to the courts." *Id.* at 316–17. *See also* Anna E. Lumelsky, *Diamond v. Chakrabarty: Gauging Congress's Response to Dynamic Statutory Interpretation by the Supreme Court*, 39 U.S.F. L. REV. 641, 658 (2005).

Discussing the statutory provisions requiring novelty and nonobviousness, the AMA's report *agrees* that patent protection for novel and nonobvious medical procedures would be "reasonable." 1995 AMA Report at 7.[15] The AMA, however, opposes patent eligibility on the grounds that "there is a significant gap between a strict interpretation of novel and non-obvious and the way that these terms are currently applied in assessing patent applications." *Id.* In the AMA's view, the PTO "has applied the statutory rules too broadly, resulting in unduly expansive patenting decisions." *Id.* The AMA's report concludes that "while the ethical problems with patenting might be solved in theory by drawing a distinction between inappropriate and appropriate medical process patents, such a solution is not useful in practice." 1995 AMA Report at 8.

To the extent the PTO is not advancing the evident purpose of the statutory nonobviousness and

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[15] Section 102 of the Patent Act forecloses a patent if the "invention was known or used by others" 35 U.S.C. §§ 102(a) and (f). Section 103 withholds patent protection for inventions that would have been obvious to a person skilled in the art at the time the invention was made. 35 U.S.C. § 103(a).

novelty requirements, the AMA's complaint is with the Executive or, failing that, Congress. These administrative complaints are not a basis to misconstrue 35 U.S.C. § 101. Section 101 is "only a threshold test" that "defines the subject matter that may be patented" and leaves the fact-intensive analyses of novelty, nonobviousness, and written description to the Act's substantive "'conditions and requirements.'" *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting §101). The "only role of Section 101" is to "identify the types of subject matter that may be *eligible* for patent protection if "'the conditions and requirements'" of Title 35 are satisfied. U.S. Br. at 31. It falls to the other provisions to make "more nuanced factual distinctions" between those inventions worthy of patent protection and those that are not. *Id.* at 32.

Physicians also have a duty to avoid costs where possible, particularly where lifesaving care is not widely available. Average prices of new drug products have been rising much faster than the rate of inflation. CBO Report at 1. Likewise, medical procedures are expensive. Burch at 1143. But concerns about cost and access, while serious, should be addressed to either the Executive or Congress.

The Executive can address the problem of access to expensive patented medical processes in a variety of ways. It can provide subsidies, tax breaks, or various other forms of financial assistance. Or it can appropriate a patent itself and compensate the patent holder after the fact. *See* Daniel R. Cahoy, *Treating the Legal Side Effects of Cipro: A Reevaluation of Compensation Rules for Government*

Takings of Patent Rights, 40 AM. BUS. L.J. 125, 139-46 (2002). Some agencies have even made patent appropriations part of their official policies. *Id.* at 136, n. 47.

Alternatively, Congress is well-equipped to address the full range of patent-related ethical concerns, including "particular complaints about the perceived unfairness of applying a general legal standard to [medicine]." *See* Dan L. Burk and Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1631 (2003) (describing Congressional interventions lengthening patent terms for pharmaceuticals, protecting generic drug suppliers from liability for certain experimental uses, protecting physicians from infringement claims, and relaxing the obviousness standard for biotechnological processes). For example, in the America Invents Act Congress decided to prohibit patents on human organisms.[16] Other examples abound, and reflect the variety of practical problems policymakers are able to address. *See, e.g.*, Physician's Immunity Statute;[17] Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act);[18] Orphan Drug Act;[19] Best

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[16] Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 33 (a), 125 Stat. 284 (2011).

[17] Pub. L. No. 104-208, §616, 110 Stat. 3009, (codified at 35 U.S.C. § 287(c) (1996)).

[18] Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified at 21 U.S.C. §§ 355, 360(cc) (2006), 35 U.S.C. §§ 156, 271, 282 (2006)), as amended by Title IX of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, 117 Stat. 2066 (codified as amended at 21 U.S.C. § 355(j)(5)(C)(i) (2006) and 35 U.S.C. § 355271(e)(5) (2006)).

Pharmaceuticals for Children Act.[20] To the extent medical process patents raise unique cost-related or other ethical concerns, Congress is free to act.

CONCLUSION

For the reasons set forth above, this Court should conclude that medical diagnostic and treatment methods are patentable subject matter.

Respectfully submitted,

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[19] Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. § 360aa-ee (1998)).

[20] Pub. L. No. 107-109, 115 Stat. 1408 (codified as amended in sections of 21 U.S.C. and 42 U.S.C.).

APPENDIX

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AMICUS CURIAE BRIEF

No. 10-1150

In The
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(d/b/a Mayo Medical Laboratories)
and MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF THE INTELLECTUAL PROPERTY AMICUS BRIEF CLINIC OF THE UNIVERSITY OF NEW HAMPSHIRE SCHOOL OF LAW AS AMICUS CURIAE IN SUPPORT OF RESPONDENT

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INTEREST OF AMICUS CURIAE[1]

The University of New Hampshire School of Law (UNHLaw, formerly Franklin Pierce Law Center) has a long history of intellectual property expertise. The intellectual property faculty of UNHLaw has filed amicus briefs for this Court as well as lower courts. UNHLaw has an established Intellectual Property Amicus Brief Clinic. With faculty guidance and student participation, the Clinic seeks to file amicus briefs that will lead to the development and predictable application of intellectual property law to promote innovation and competition. The Clinic submits briefs for selected cases with the hopes of contributing important perspectives that might not be adequately represented by the parties.

INTRODUCTION

The question presented in this case is the scope of patent-eligible subject matter under 35 U.S.C. § 101. The court below in *Prometheus* found that the claims at issue had two transformations and thus

[1] The parties have lodged blanket letters of consent to the filing of amicus briefs with the Clerk of the Court. The parties have been notified of the filing of our amicus briefs. No counsel for a party authored this brief in whole or in part, and no person other than *amicus curiae*, its members or its counsel made a monetary contribution to its preparation or submission.

met the "machine-or-transformation" test.[2] *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347 (Fed. Cir. 2010). When claims are found to meet the machine-or-transformation test, it is highly likely that they are *not* directed to an abstract idea or law of nature.[3] This Court found the machine-or-transformation test to be "a useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101." *Bilski v. Kappos*, 130 S. Ct. 3218, 3227 (2010). The issue here is the scope of the judicial exceptions to patent-eligible subject matter of method claims.

On the issue of patent eligibility under 35 U.S.C. § 101, we believe that the decision below is correct. Two different panels of the Court of Appeals for the Federal Circuit have found that Prometheus's claims

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[2] While we use the term "machine-or-transformation" as shorthand to describe a test for the patent-eligibility of a process, the approach is a bit more sophisticated. The method must involve a "particular" machine or it must involve the transformation of "an article to a different state or thing." *See Diamond v. Diehr*, 450 U.S. 175, 192-93 (1981) (particular machine); *Expanded Metal Co. v. Bradford*, 214 U.S. 366, 384 (1909) (transformation). Further, the transformation cannot be trivial, it must be central to the purpose of the process. *See In re Bilski*, 545 F.3d 943, 962 (Fed. Cir. 2008).

[3] The amicus brief of the New York Intellectual Property Law Association urges: "that in order for the machine-or-transformation test to remain a useful tool, the Section 101 inquiry must end when the test is *met*." We do not go that far. Some flexibility is still needed to account for the creativity of future patent application drafters. We believe that the "highly likely" language is sufficient.

include steps involving "transformations" and that the transformations are central to the purpose of the claimed process.[4] The claims would also be patent eligible under the approach we propose. We take no position on whether the claims meet any other requirements of the statute.

However, there continues to be an opportunity to define a comprehensive approach to determine what constitutes a patent-eligible process. Judge Rader recognized this blank spot in the recent *Ultramerical* decision, quoting Justice Stevens as stating, "[t]he Court . . . [has] never provide[d] a satisfying account of what constitutes an unpatentable abstract idea." *Ultramerical, LLC v. Hulu, LLC*, No. 2010-1544, 2011 WL 4090761, at *4 (Fed. Cir. Sept. 15, 2011). This brief proposes an approach that is more general than the machine-or-transformation test and a) is in keeping with this Court's precedents in *Cochrane v. Deener*, 94 U.S. 780 (1876); *Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584 (1978); and *Diehr*, 450 U.S. 175; and b) is flexible enough to apply to new types of technology that will be developed in the future. A more comprehensive approach would benefit federal courts, the U.S. Patent and Trademark

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[4] Judge Lourie wrote both opinions below. The panel in the first opinion consisted of Judge Lourie, Judge Michel (then Chief Judge), and District Judge Clark. *Prometheus Labs. Inc. v. Mayo Collaborative Servs.*, 581 F.3d 1336, 1339 (Fed. Cir. 2010). The panel in the decision on remand after this Court's decision in *Bilski v. Kappos* consisted of Chief Judge Rader, Judge Lourie, and Judge Bryson. *Prometheus*, 628 F.3d at 1349.

Office ("PTO"), and inventors by differentiating between patent eligible processes and patent ineligible processes.

SUMMARY OF THE ARGUMENT

In the decision below, the Federal Circuit held that a method for optimizing therapeutic efficacy that includes the steps of administering a drug into a subject, and determining the level of the drug's metabolite is patent eligible under 35 U.S.C. § 101. This Court has repeatedly confirmed that Congress intended § 101 to be interpreted broadly, acting more as a threshold check as opposed to a substantive bar to patentability. In this regard, the Federal Circuit has followed this Court's interpretation of the statute.

U.S. Patent 6,355,623 ("the '623 patent") meets the standards set forth in this Court's precedents for 35 U.S.C § 101 patent eligibility. The Federal Circuit was correct in ruling that the Prometheus claim is drawn to patent-eligible subject matter because it meets the transformation prong of the machine-or-transformation test.

Our proposed comprehensive two-step approach is to first identify whether the claim specifies *how* to achieve a result. If the claim does so, then the second step is to determine if the claim refrains from wholly preempting the use of a judicial exception, such as a law of nature. If the claim does not preempt any judicial exceptions, then it is patent eligible. This

approach is consistent with the precedent this Court has set in *Benson*, 409 U.S. 63; *Flook*, 437 U.S. 584; *Diehr*, 450 U.S. 175; and *Bilski* 130 S. Ct. 3218.

ARGUMENT

I. Legal Background

a. 35 U.S.C. § 101 is Designed to be a Coarse Filter

The States have granted to the Federal Government the authority to establish a patent system. U.S. CONST. art. I, § 8, cl. 8. The scope of that authority has few limits. Congress has responded with a patent statute that is expansive in defining patent-eligible subject matter. 35 U.S.C. § 101 sets forth the categories of subject matter that are eligible for patent protection: "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." This Court has repeatedly confirmed the broad scope of § 101: "[i]n choosing such expansive terms modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Bilski*, 130 S. Ct. at 3225 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980)).

b. Congress has Essentially Chosen to Leave 35 U.S.C. § 101 Alone

On September 16, 2011, President Obama signed the America Invents Act ("AIA"). Amid the continuing controversy over the scope of patent-eligible subject matter in the courts, Congress made no changes to 35 U.S.C. § 101. Thousands of patents have issued over the years in the area of business methods, medical treatment and isolated genes. In the AIA, there are only two sections that address patent eligibility and neither modify § 101. Section 14 of the Act is a stand-alone provision wherein "tax strategies" are deemed to be in the prior art.[5] Section 33 is a stand-alone

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[5] America Invents Act § 14, Tax Strategies Deemed Within the Prior Art (2011).

> (a) IN GENERAL. – For purposes of evaluating an invention under section 102 or 103 of title 35 United States Code, any strategy for reducing, avoiding, or deferring tax liability, whether known or unknown at the time of the invention or application for patent, shall be deemed insufficient to differentiate a claimed invention from the prior art.
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> (b) DEFINITION. – For purposes of this section, the term "tax liability" refers to any liability for a tax under any Federal, State, or local law, or the law of any foreign jurisdiction, including any statute, rule, regulation, or ordinance that levies, imposes, or assesses such tax liability.
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> (c) EXCLUSIONS. – This section does not apply to that part of an invention that
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> > (1) is a method, apparatus, technology, computer program product, or system, that is used solely for preparing a tax or information return or other

(Continued on following page)

section prohibiting patenting of human organisms.[6] The only other statutory limitation on patent eligibility is found, not in the patent statute, but in the Atomic Energy Act of 1954 which eliminates patent eligibility for "any invention or discovery which is useful solely in the utilization of special nuclear material or atomic energy in an atomic weapon."[7] Congress is clearly aware of the controversies surrounding patent eligibility and has chosen to craft narrow solutions to minimize and resolve these controversies.

Responding to competing policy forces is the unique province of Congress. This Court has on several occasions been confronted with a "gruesome

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> tax filing, including one that records, transmits, transfers, or organizes data related to such filing; or
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> (2) is a method, apparatus, technology, computer program product, or system used solely for financial management, to the extent that it is severable from any tax strategy or does not limit the use of any tax strategy by any taxpayer or tax advisor.
>
> (d) RULE OF CONSTRUCTION. – Nothing in this section shall be construed to imply that other business methods are patentable or that other business method patents are valid.

[6] *Id.* at § 33, Limitation on Issuance of Patents. "(a) LIMITATION. – Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism."

[7] Atomic Energy Act of 1954, 42 U.S.C. § 2181(a) (2011).

parade of horribles." *Chakrabarty*, 447 U.S. at 316. The Court has, correctly in our opinion, noted:

> What is more important is that we are without competence to entertain these arguments – either to brush them aside as fantasies generated by fear of the unknown, or to act on them. The choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot. That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives. Whatever their validity, the contentions now pressed on us should be addressed to the political branches of the Government, the Congress and the Executive, and not to the courts.

Id. at 317.

This Court has dealt with the issue of patent eligibility of processes for more than 100 years. In *Cochrane*, the invention related to a process for increasing the quality of flour. 94 U.S. at 787-88. This Court defined "process" quite broadly: "[a] process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject-matter to be transformed and reduced to a different state or thing." *Id.* When faced with the argument that a process must meet the machine-or-transformation test, this Court broadened even the expansive statement in *Cochrane*: "We do

not hold that no process patent could ever qualify if it did not meet the requirements of our prior precedents." *Benson*, 409 U.S. at 71; *see Bilski*, 130 S. Ct. at 3258.

Unfortunately, defining what is patent eligible and what is not has been a vexing problem. This Court has established only three judicial exceptions to Congress' broad statement of patent eligibility: "laws of nature, physical phenomena, and abstract ideas." *Bilski*, 130 S. Ct. at 3225. However, these exceptions can be difficult to apply. For example, in *Bilski*, Justice Stevens acknowledged that "[t]he Court . . . [has] never provide[d] a satisfying account of what constitutes an unpatentable abstract idea." *Id.* at 3236.

There are currently various approaches to analyze the patent eligibility of a process, some of which arise from the guidance of this Court in *Cochrane*, 94 U.S. 780; *Benson*, 409 U.S. 63; *Flook*, 437 U.S. 584; and *Diehr*, 450 U.S. 175. One approach establishes that a process is *not* patent eligible if it is a series of purely mental steps, in other words, a process that can be carried out entirely in the human mind. *See Benson*, 409 U.S. at 67. Another approach finds a process is *not* patent-eligible if it wholly preempts a mathematical algorithm. *Flook*, 437 U.S. at 587. A further approach finds a process *is* (very likely

to be) patent eligible if it meets the machine-or-transformation test.[8]

Unfortunately, each of these approaches provides limitations and definitions for only a narrow subset of patent-eligible processes but leaves some processes unaddressed. For example, this Court in *Bilski* acknowledged that processes not satisfying the machine-or-transformation test could be patent eligible. Therefore, there is a need for a comprehensive approach to determine what constitutes a patent-eligible process. By providing a comprehensive approach, this Court would allow the eligibility of any process claim currently under examination at the PTO[9] or in litigation[10] to be more easily decided

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[8] We have not been able to find a case where the process was found to meet the machine-or-transformation test but was found to be NOT patent eligible.

[9] *See generally Ex parte Gesek*, No. 2009-009424, 2011 WL 891748 (B.P.A.I., Mar. 10, 2011); *Ex parte Asare*, No. 2009-007451, 2010 WL 4917801 (B.P.A.I., Nov. 17, 2010); *Ex parte Hunleth*, No. 2009-005621, 2010 WL 4601413 (B.P.A.I., Nov. 10, 2010); *Ex parte Mackenzie*, No. 2009-007332, 2010 WL 3922193 (B.P.A.I., Oct. 5, 2010).

[10] *See generally CLS Bank Int'l v. Alice Corp.*, 768 F. Supp. 2d 221 (D.D.C. 2011), *appeal docketed*, No. 2011-1301 (Fed. Cir., Apr. 8, 2011); *Fort Props., Inc. v. Am. Master Lease, LLC*, 609 F. Supp. 2d 1052 (C.D. Cal. 2009), *stay of appeal lifted*, No. 2009-1242 (Fed. Cir., Dec. 1, 2010); *DealerTrack, Inc. v. Huber*, 657 F. Supp. 2d 1152 (C.D. Cal. 2009), *stay of appeals lifted*, No. 2009-1566 and No. 2009-1588 (Fed. Cir., Oct. 4, 2010); *FuzzySharp Techs., Inc. v. 3D Labs Inc.*, No. C 07-5948 SBA (N.D. Cal., Dec. 11, 2009), *stay of appeal lifted*, No. 2010-1160 (Fed. Cir., Mar. 25, 2010).

without waiting for the Federal Circuit to define additional criteria for determining what constitutes a patent-eligible process.[11]

c. 35 U.S.C. § 101 Should be Applied to the Claim as a Whole

A consistent theme in this Court's decisions is that the claims of the invention at issue should be considered *as a whole* in a variety of contexts, and in particular where the issue is patent eligibility. This dictates that claims should not be parsed, looking only for steps that are, alone, judicially excepted subject matter. The claim should be viewed as a whole, and it is "inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Diehr*, 450 U.S. at 188. Further, "[o]ur conclusion regarding respondents' claims is not altered by the fact that in several steps of the process a mathematical equation and a programmed digital computer are used." *Id.* at 185. Even if particular steps are not patent eligible when standing alone, this Court has recognized that "an

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[11] *See SciMed Life Sys. Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1347 (Fed. Cir. 2001) (Dyk, J., concurring) (alluding to the need for the court to provide rules of decision regarding claim construction for clarity and predictability); *CVI/Beta Ventures, Inc. v. Tura LP*, 120 F.3d 1260, 1261 (Fed. Cir. 1997) (Mayer, J., dissenting) (suggesting that when members of the court create exceptions in the decision making process, they encumber the process with ambiguity and uncertainty).

application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 188). Therefore, any comprehensive approach should be applied to the claim as a whole.

d. 35 U.S.C. § 101 Should be Applied Divorced from Other Statutory Considerations

We urge the Court not to infuse the patent eligibility analysis with other patentability considerations that are better suited for consideration under more appropriate provisions of the statute. For example, just because a claim is extremely broad does not mean that it is not directed to patent eligible subject matter.[12] These problems with claim scope are better resolved under, for example, the enablement requirement of 35 U.S.C. § 112. Claims that belong to a category of inventions that some believe are of "suspect validity" does not necessarily mean that the claim is not patent eligible at the threshold. *Bilski*, 130 S. Ct. at 3229. Validity concerns are better resolved, for example, under the standard for non-obviousness of 35 U.S.C. § 103. This is particularly true after this Court's decision in *KSR International*

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[12] This is analogous to the Courts recognition that: "Broad general language is not necessarily ambiguous when Congressional objectives require broad terms." *Chakrabarty*, 447 U.S. at 315.

Co. v. Teleflex Inc., 550 U.S. 398 (2007). This decision is widely recognized as tightening the obviousness standard. *See generally* Jennifer Nock & Sreekar Gadde, *Raising the Bar for Nonobviousness: An Empirical Study of Federal Circuit Case Law Following KSR*, SOCIAL SCIENCE RESEARCH NETWORK, May 5, 2010, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1612052.pdf. Just because a claim recites an old element (hedging in *Bilski* – not patent eligible; the Arrhenius equation in *Diehr* – patent eligible) does not indicate that the claim is directed to patent ineligible subject matter. *See Bilski*, 130 S. Ct. at 3229; *Diehr*, 450 U.S. at 178. Questions regarding the novelty of an invention are better analyzed under 35 U.S.C. § 102.

II. The Court Should Provide a Comprehensive Approach to Determine What Constitutes a Patent-Eligible Process

In *Bilski*, this Court rejected the machine-or-transformation test as an exclusive test and directed the Federal Circuit to develop additional, yet undefined, criteria for determining what constitutes a patent eligible process. 130 S. Ct. at 3222-23. This Court has identified useful and important clues for determining whether a claimed process is directed to patent-eligible subject matter, but has not comprehensively defined what constitutes a patent-eligible process. Such clues may include determining whether

a process is tied to a particular machine or determining whether a process transforms a particular article into a different state or thing. *Id.* at 3224. However, there is a gray area for processes in which a machine or a transformation may be absent. When a claimed process falls in this gray area, it creates uncertainty for patentees and infringers regarding whether the process is patent eligible under § 101.

Therefore, rather than developing a multitude of tests, each of which must be consulted as "clues" for determining the patent eligibility of a process, this Court should develop a more comprehensive approach. *See id.* This brief presents an approach that is grounded in this Court's precedents and clearly defines when a process *is* patent eligible. This approach for patent eligibility of a process greatly reduces the present uncertainty for patentees and potential infringers surrounding process claims.

a. We Propose that a Claim is Patent Eligible When the Claim Specifies *How* to Achieve a Result and Refrains from Preempting All Uses of a Judicial Exception

We propose a comprehensive approach for determining the patent eligibility of a process. The approach is a two-step analysis as shown in Figure 1 and is further described below.

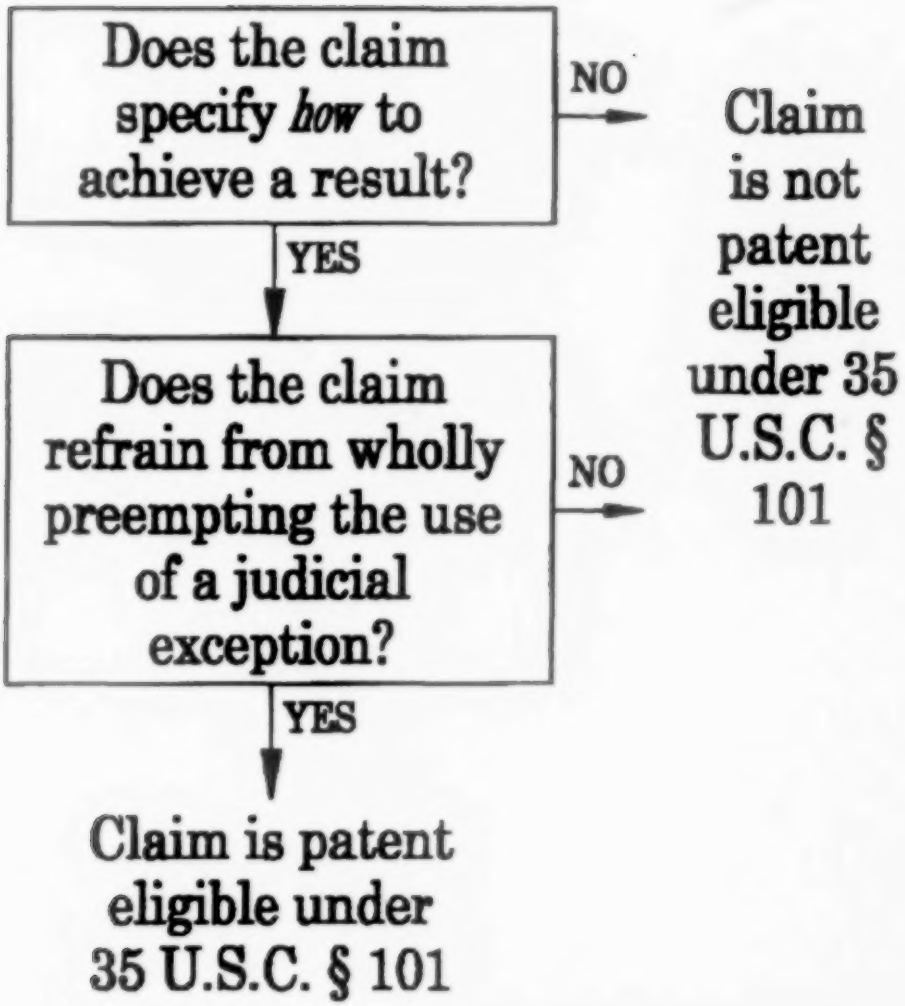

Figure 1: Proposed Comprehensive Approach

First, does the claim specify how to achieve a result? The result itself may be specified explicitly or implicitly; however, the manner by which the result is achieved must be explicitly recited in one or more steps. If the claim fails to describe *how* to achieve the results, the claim is *not* patent eligible. In other words, a claim is not patent eligible when it is missing details regarding *how* to achieve a result.

Second, if the claim describes *how* to achieve the results, does the claim refrain from wholly preempting the use of a judicial exception? Even if the claim specifies how to achieve the results, the claim cannot be patent eligible if it wholly preempts the use of a judicial exception, such as a mathematical algorithm or a process consisting solely of mental steps. Thus, if the claim specifies how to achieve the results and the claim does not wholly preempt the use of a judicial exception, the claimed process is patent eligible under § 101.

This analysis provides a comprehensive approach to determine the patent eligibility of a process and, as a result, it eliminates the current gray area of patent eligibility of a process. For example, if a process fails the machine-or-transformation test, the patent eligibility of the process can still be determined by applying the two-step analysis described above. If a claim that fails the machine-or-transformation test specifies *how* to achieve a result and refrains from wholly preempting all uses of a judicial exception, then the claim is patent eligible under § 101. Thus, by using a comprehensive approach to define patent eligibility, the eligibility of any process can be determined using a clear analytical framework and without requiring the Federal Circuit to define additional criteria.[13]

In summary, a claim for a process is patent eligible when it specifies *how* to achieve a result and

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[13] *See supra* text accompanying note 11.

refrains from wholly preempting all uses of a judicial exception. If the claim does not specify *how* to achieve the results, then the claim is not patent eligible under § 101. In the alternative, if the claim specifies *how* to achieve the results, but wholly preempts all use of a judicial exception, the claim is also not patent eligible. This approach for eligibility of a process claim is consistent with this Court's precedent.

III. Application of the Comprehensive Approach to this Court's Precedent

a. With respect to *Bilski v. Kappos*, 130 S. Ct. 3218 (2010)

The claims at issue in *Bilski* were directed to a "method for managing the consumption risk costs of a commodity sold by a commodity provider at a fixed price."[14] Petition for Writ of Certiorari, *Bilski v. Doll*, 129 S. Ct. 2735 (2009) (No. 08-964), 2009 WL 226501 at *7-8. This Court found that Bilski's claims were not patent eligible because "the concept of hedging, described in claim 1 and reduced to a mathematical formula in claim 4, is an unpatentable abstract idea. . . ." *Bilski*, 130 S. Ct. at 3231. In deciding *Bilski*, this Court reaffirmed that 35 U.S.C. § 101 should "be given wide scope," *id.* at 3225, and that, rather than imposing "atextual," *id.* at 3229, limitations, patent-eligible processes should be defined by

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[14] This Court has referred to Bilski's claim 1 as a method instructing how to hedge risk. *Bilski*, 130 S. Ct. at 3223.

35 U.S.C. § 100(b) and by "looking to the guideposts in *Benson*, *Flook*, and *Diehr*." *Id.* at 3227, 3231. However, after applying those guidepost cases, this Court found that the claims in *Bilski* were not patent eligible because they were drawn to the abstract idea of hedging risk or a mathematical expression thereof. *Id.* at 3229-31. This Court further held that limiting use of the idea to the "particular technological environment," of energy markets was insufficient to create patent eligibility. *Id.* at 3229-30.

Bilski's claims are also not patent eligible under our proposed comprehensive approach for determining the patent eligibility of a process. The purported result achieved by the claims in *Bilski* is "managing the consumption risk costs of a commodity sold by a commodity provider at a fixed price." Petition for Writ of Certiorari, 2009 WL 226501 at *7-8. To achieve this result, claim 1 recites a method having three steps:

> (a) initiating a series of transactions between said commodity provider and consumers of said commodity wherein said consumers purchase said commodity at a fixed rate based upon historical averages, said fixed rate corresponding to a risk position of said consumers;
>
> (b) identifying market participants for said commodity having a counter-risk position to said consumers; and
>
> (c) initiating a series of transactions between said commodity provider and said market participants at a second fixed rate such that said series of market participant

> transactions balances the risk position of said series of consumer transactions.

Bilski, 130 S. Ct. at 3223-24.

The shortcoming of this claim is that these elements do not specify *how* one would go about initiating transactions, identifying consumers, identifying market participants with a counter-risk position, determining historical averages, or corresponding the risk position of the consumer with a fixed rate. In other words, because claim 1 does not specify *how* to achieve the intended result, it cannot be patent eligible under the first step of our proposed comprehensive approach.

On the other hand, claim 4 of Bilski's application does recite more specific details regarding *how* to achieve the intended result and, therefore, would likely satisfy the first prong of our proposed comprehensive approach. Petition for Writ of Certiorari, 2009 WL 226501 at *7-8. However, all of the specifics provided in claim 4 are merely numerical inputs which are then combined into an abstract mathematical algorithm. This Court recognized that enforcing such a claim would be tantamount to "allowing petitioners to patent risk hedging [and] pre-empt use of this approach in all fields. . . ." *Bilski*, 130 S. Ct. at 3231. Accordingly, this claim would not be patent eligible because it does not, as required by the second step of our proposed comprehensive approach, refrain from wholly preempting the use of a judicial exception. Bilski's claims actually preempt the use of two

different abstract ideas, both the abstract concept of hedging risk and the abstract mathematical formula used to execute that concept. *Id.* at 3223.

Thus, our proposed comprehensive approach for determining the patent eligibility of a process operates in accordance with this Court's decision in *Bilski* and, as further discussed below, is also consistent with "the guideposts in *Benson*, *Flook*, and *Diehr*." 130 S. Ct. at 3231.

b. With Respect to Guidepost Case *Gottschalk v. Benson*, 409 U.S. 63 (1972)

In *Benson* this Court held that claims directed to a method for converting numeric data from binary coded decimal (BCD) numerals into pure binary numerals using a general-purpose computer were not patent-eligible subject matter under 35 U.S.C. § 101. *Benson*, 409 U.S. at 68, 71. This Court explained that, while an abstract idea such as a mathematical formula is not patent-eligible subject matter by itself, a novel and useful structure or process that is created with the aid of a mathematical formula and practically applies the formula can be patent-eligible subject matter. *Id.* at 67.

However, even a practical application must refrain from covering every use of a judicial exception, because the practical effect of such a claim would be to wholly preempt the use of the exception and in essence be a patent on the exception itself. *Id.* at 71.

The proposed comprehensive approach is consistent with this Court's holding in *Benson*. Benson's claim 13 explicitly states the intended result of a "data processing method for converting binary coded decimal number representations into binary number representations." (*See* Appendix at A-2). The body of claim 13 describes the steps to be performed on the BCD numbers, such as testing binary positions, and explains the conditions under which a step would be repeated in sufficient detail to obtain the required result of binary numbers, and hence specifies *how* to achieve the intended result. Therefore, claim 13 satisfies the first step of our comprehensive approach.

The second step of our comprehensive approach requires a determination of whether the claim refrains from wholly preempting the use of a judicial exception. Here, claim 13 *preempts* the use of a mathematical formula because, although the claim explains *how* the result of the claim is to be achieved, the claim preempts the concept of conversion of BCD numerals to binary numerals. That is, a person performing the method of claim 13 manually (either on paper, or mentally) or using any sort of computing device would infringe the claim. Hence, the scope of the claim is so broad that it preempts all known and unknown uses of converting BCD numerals to binary numerals. Accordingly, claim 13 preempts all use of a judicial exception, here an abstract idea represented by a mathematical formula, and therefore cannot be patent-eligible subject matter under this Court's precedent or our proposed comprehensive approach.

The *Benson* Court also deemed that claim 8 of the application, which recites a method for converting signals from BCD form into binary form using a reentrant shift register, was not patent-eligible subject matter under 35 U.S.C. § 101. *Benson*, 409 U.S. at 71-72; (*see* Appendix at A-1). Possibly, this ruling may have been a result of the limited understanding of computers in 1972, because under the *Benson* Court's holdings, the machine-or-transformation test, or our proposed comprehensive analysis, this claim would likely be considered patent-eligible subject matter today. Claim 8 recites a particular machine, i.e., a reentrant shift register, which must be operated in a specific sequence of steps, satisfying the machine-or-transformation test. This is an "important clue" that claim 8 should be patent eligible. *See Bilski*, 130 S. Ct. at 3227. Even this Court's holding in *Benson* dictates that claim 8 should be patent eligible. 409 U.S. at 71-72. Specifically, Benson's claim 8 does not preempt a mathematical algorithm because the claimed process cannot be performed without the use of a specialized machine, a reentrant shift register, which must be operated by executing a particularized sequence of steps.

Applying our comprehensive analysis to Benson's claim 8, the claim explicitly states the objective or result of the claim in its preamble reading "the method of converting signals from binary coded decimal form into a binary." (*See* Appendix at A-1). Further, the claim requires performance of tasks such as storing the signals in a shift register, shifting the signals,

masking, and adding signals, to ultimately obtain the required binary signal. In doing so, the claim recites the use of a reentrant shift register (i.e. a particular machine) to obtain the desired result. Therefore, because the above claim specifies exactly *how* to achieve the intended results, (by storing, shifting, masking and adding to finally obtain the binary signal using a reentrant shift register), claim 8 satisfies the first step of our comprehensive analysis.

Under the second step of our comprehensive analysis, and in accordance with this Court's analysis in *Benson*, claim 8 *does not preempt* the use of a judicial exception because the claim applies only to converting BCD to binary by executing a specific series of steps on a particular type of machine, a reentrant shift register. Therefore, we submit that claim 8 is patent-eligible subject matter under both this Court's analysis in *Benson* and our proposed comprehensive analysis.

It is not our position that this Court's holding in *Benson* be overruled because the holding that a claim preempting a judicial exception should not be patent-eligible subject matter is correct. We agree that allowing such a claim would be granting a monopoly on the idea itself and would be contrary to the spirit of U.S. Patent Law. *See Benson*, 409 U.S. at 72. However, claim 8 of the patent in *Benson*, requiring a reentrant shift register to be operated in a specific way, clearly satisfies the machine-or-transformation test, our proposed comprehensive approach, and this Court's precedent in *Benson* itself. Therefore, claim 8

is patent eligible when analyzed in a manner consistent with the law as we know it today.

c. With Respect to Guidepost Case *Parker v. Flook*, 437 U.S. 584 (1978)

Flook involved a patent that claimed a "Method for Updating Alarm Limits" and "the only novel feature of the method [was] a mathematical formula." 437 U.S. at 585. The method includes three steps: "an initial step which merely measures the present value of the process variable (e.g., the temperature); an intermediate step which uses an algorithm to calculate an updated alarm-limit value; and a final step in which the actual alarm limit is adjusted to the updated value." *Id.* This Court stated that the patent only provides "a *formula* for computing an updated alarm limit." *Id.* at 586 (emphasis added).

In deciding *Flook*, this Court referred to *Benson*. *Flook*, 437 U.S. at 592. The claims in *Benson* were found not patent eligible because "an algorithm, or mathematical formula, is like a law of nature, [and] *Benson* applied the established rule that a law of nature cannot be the subject of a patent." *Id.* at 589. Flook argued that his claims were distinguishable from Benson's and were patent eligible because of the "'post-solution' activity [of] the adjustment of the alarm limit to the figure computed according to the formula." *Id.* at 590. This Court disagreed and found "[t]he notion that post-solution activity, no matter how conventional or obvious in itself, can transform

an unpatentable principle into a patentable process exalts form over substance. A competent draftsman could attach some form of post-solution activity to almost any mathematical formula. . . ." *Id.* This Court further found that "an inventive application of the principle may be patented" but Flook's patent application "simply provides a new and presumably better method for calculating alarm limit values." *Id.* at 594-95. Because of the stated reasoning, this Court found Flook's claims were not patent eligible under § 101.

Under our comprehensive approach, Flook's claims are also not patent-eligible subject matter. The first step of our approach states that a claim is patent eligible if the claim specifies *how* to achieve a result. The result that the claims in *Flook* purport to achieve is updating the value of an alarm limit. To achieve this result, the claim recites "determining the present value of said process value . . . determining a new alarm base B1 using [an] equation . . . determining an updated alarm limit which is defined as B1 + K . . . adjusting said alarm limit to said updated alarm limit value." (*See* Appendix at A-3). However, the claim gives no information as to *how* one would go about determining the present process value, which is used in determining the other variables. Furthermore, the claim recites various equations, but does not specify *how* to determine the variables in those equations.

This Court recognized the lack of specificity and stated:

> The patent application does not purport to explain *how* to select the appropriate margin of safety, the weighting factor, or any of the other variables. Nor does it purport to contain any disclosure relating to the chemical processes at work, the monitoring of process variables, or the means of setting off an alarm or adjusting an alarm system.

Flook, 437 U.S. at 586 (emphasis added). Therefore, the claim only describes the invention in terms of results without specifying how to achieve those results, and the claim is not patent eligible under § 101.

d. With Respect to Guidepost Case *Diamond v. Diehr*, 450 U.S. 175 (1981)

In *Diehr*, this Court determined that a process claim for curing synthetic rubber was patent-eligible subject matter under 35 U.S.C. § 101. 450 U.S. at 193. The process claim at issue was directed to the use of a computer to constantly measure the temperature of a mold, constantly recalculate the cure time, and then open the mold at the appropriate time, resulting in a cured rubber product. *Id.* at 179; (*see* Appendix at A-4). The patent examiner had rejected the claims because the claimed process was carried out on a computer containing a program. *Id.* The Patent and Trademark Office Board of Appeals agreed with the examiner, but the Court of Customs and Patent Appeals reversed the finding that the presence of a computer does not make a claim patent ineligible subject matter. *Id.* at 181.

This Court affirmed the decision of the Court of Customs and Patent Appeals and found that the process was patent eligible. *Id.* at 193. In making this determination, this Court first resolved that the process fell within one of the categories of patent-eligible subject matter. *Id.* at 183-84. In support of this finding, this Court stated:

> That respondents' claims involve the transformation of an article, in this case raw, uncured synthetic rubber, into a different state or thing cannot be disputed. The respondents' claims describe in detail a step-by-step method for accomplishing such, beginning with the loading of a mold with raw, uncured rubber and ending with the eventual opening of the press at the conclusion of the cure. Industrial processes such as this are the types which have historically been eligible to receive the protection of our patent laws.

Id. at 184.

This Court also found that the inclusion of some subject matter that is directed to a judicially created exception does not necessarily render a claim patent ineligible. *Id.* at 187. For example, a patent-eligible claim may use a mathematical equation or a computer program, or may apply a law of nature. *Id.* The claimed process for curing synthetic rubber, evaluated as a whole, was directed to an industrial process for molding rubber products that happened to use a mathematical formula. *Id.* at 191-93. The claim did not preempt the use of the mathematical formula in

other applications. *Id.* at 187. Based on the above analysis, this Court found the process patent eligible. *Id.* at 193.

Our proposed comprehensive approach for evaluating the patent eligibility of a process produces a result consistent with this Court's decision in *Diehr*. Diehr's claim 1 satisfies the first step of our comprehensive approach because the claim sufficiently specifies *how* to achieve a result. The preamble of claim 1 states, "[a] method of operating a rubber molding press for precision molded compounds with the aid of a digital computer. . . ." (*See* Appendix at A-4). This preamble communicates the intended result of practicing the method delineated in claim 1. With this result in mind, the claim describes *how* to operate a rubber molding press. The body of the claim provides, in summary, properties to be input that are consistent with the compound being molded, placement of a timer and when it should be initiated, determination of the temperature in the mold, communication of the temperature to the computer, use of an equation to determine a reaction time, a comparison of the computer calculated time to the total elapsed time, determination of when the press should be opened based on the comparison, and opening of the press. (*See* Appendix at A-4). Each step adds to the previous step, so that the claim as a whole explains to a person skilled in the art *how* to operate the rubber molding press. Thus, the claim adequately communicates *how* to achieve the result stated in the preamble. Accordingly, claim 1 satisfies the first step of our approach.

The claim must now be analyzed under the second step.

Applying the second step of our approach, the claim refrains from wholly preempting the use of a judicial exception. The judicial exception at issue in *Diehr* was an abstract algorithm. This Court defined the algorithm or mathematical equation as similar to a law of nature. *Diehr*, 450 U.S. at 186. In claim 1, the mathematical equation is used in a single step to calculate the reaction time during the curing process. Viewing the claim as a whole, this Court acknowledged that the mathematical equation *must* be performed with the other steps of the claim. Thus, the claim would only restrict the use of the mathematical equation when used in conjunction with the other steps of claim 1 to produce a cured rubber product and does not preempt the equation for other uses. Therefore, claim 1 is patent eligible subject matter in view of the second step of our approach because it refrains from wholly preempting the use of a judicial exception.

In conclusion, claim 1 specifies a result and *how* to achieve that result and refrains from wholly preempting the use of a judicial exception. Consistent with the decision of this Court, claim 1 is directed to patent-eligible subject matter based on the application of our proposed approach for evaluating the patent eligibility of a process.

IV. The Prometheus Claims are Patent Eligible Under Our Proposed Two Step Approach

The method in the Prometheus claims is "a method for optimizing therapeutic efficacy." (*See* Appendix at A-5). This is an explicit statement of the result that is desired. The Prometheus claims also describe *how* that result is to be achieved. That result is achieved by *administering* a drug (one that produces a specific metabolite) to a subject and by *determining* the level of that specific metabolite in the subject. (*See* Appendix at A-5).

The claims also do not fall within any specific judicial exception. They do not wholly preempt a mathematical algorithm nor can all of the steps be simply mental. The *administering* step is physically performed on a subject. Similarly, the *determining* step is also physically performed on a subject, typically by physically taking a sample from the blood of the subject and physically analyzing the sample. While the claims call for what might be considered to be mental steps (the "indicates a need" phrase in the two wherein clauses of the claim), the presence of other non-trivial non-mental steps makes the claims, *as a whole*, patent eligible.[15]

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[15] In *Diehr*, this Court specifically held that: "Our conclusion regarding respondents' claims is not altered by the fact that in several steps of the process a mathematical equation and a programmed digital computer are used." 450 U.S. at 185.

CONCLUSION

For the foregoing reasons, we firmly believe that this honorable Court should uphold the finding by the Federal Circuit, that the '623 patent is directed to patent-eligible subject matter. The Prometheus claims are patent-eligible subject matter under the precedence of this Court and meet the requirements of our proposed comprehensive analysis.

The proposed analysis was created in concordance with this Court's decisions in the guidepost cases *Benson*, *Flook*, *Diehr*, and *Bilski*. The two-step comprehensive approach for what constitutes an "abstract idea" not only results in the same outcome as those guidepost cases; it also subsumes the need for the machine-or-transformation test, or the practical application test. We respectfully request this Court adopt the use of our two-step comprehensive approach, and find that the subject matter of the '623 patent is patent eligible.

Respectfully submitted,

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APPENDIX

I. Claim 1 of Bilski

A method for managing the consumption risk costs of a commodity sold by a commodity provider at a fixed price comprising the steps of:

a. initiating a series of transactions between said commodity provider and consumers of said commodity wherein said consumers purchase said commodity at a fixed rate based upon historical averages, said fixed rate corresponding to a risk position of said consumer;

b. identifying market participants for said commodity having a counter-risk position to said consumers; and

c. initiating a series of transactions between said commodity provider and said market participants at a second fixed rate such that said series of market participant transactions balances the risk position of said series of consumer transactions.

II. Claims 8 and 13 of Benson

a. Claim 8 reads:

The method of converting signals from binary coded decimal form into binary which comprises the steps of:

(1) storing the binary coded decimal signals in a reentrant shift register,

(2) shifting the signals to the right by at least three places, until there is a binary '1' in the second position of said register,

(3) masking out said binary '1' in said second position of said register,

(4) adding a binary '1' to the first position of said register,

(5) shifting the signals to the left by two positions,

(6) adding a '1' to said first position, and

(7) shifting the signals to the right by at least three positions in preparation for a succeeding binary '1' in the second position of said register.'

b. Claim 13 reads:

A data processing method for converting binary coded decimal number representations into binary number representations comprising the steps of

(1) testing each binary digit position '1,' beginning with the least significant binary digit position, of the most significant decimal digit representation for a binary '0' or a binary '1';

(2) if a binary '0' is detected, repeating step (1) for the next least significant binary digit position of said most significant decimal digit representation;

(3) if a binary '1' is detected, adding a binary '1' at the (i 1)th and (i 3) th least significant binary digit positions of the next lesser significant decimal digit representation, and repeating step (1) for the next least significant binary digit position of said most significant decimal digit representation;

(4) upon exhausting the binary digit positions of said most significant decimal digit representation, repeating steps (1) through (3) for the next lesser significant decimal digit representation as **259 modified by the previous execution of steps (1) through (3); and

(5) repeating steps (1) through (4) until the second least significant decimal digit representation has been so processed.'

III. Claim 1 of Flook

A method for updating the value of at least one alarm limit on at least one process variable involved in a process comprising the catalytic chemical conversion of hydrocarbons wherein said alarm limit has a current value of

$$Bo + K$$

wherein Bo is the current alarm base and K is a predetermined alarm offset which comprises:

(1) Determining the present value of said process variable, said present value being defined as PVL;

(2) Determining a new alarm base B_1, using the following equation:

$$B_1 = Bo(1.0 - F) + PVL(F)$$

where F is a predetermined number greater than zero and less than 1.0;

(3) Determining an updated alarm limit which is defined as $B_1 + K$; and thereafter

(4) Adjusting said alarm limit to said updated alarm limit value."

IV. Claim 1 of Diehr

A method of operating a rubber-molding press for precision molded compounds with the aid of a digital computer, comprising:

a. providing said computer with a data base for said press including at least, natural logarithm conversion data (ln), the activation energy constant (C) unique to each batch of said compound being molded, and a constant (x) dependent upon the geometry of the particular mold of the press,

b. initiating an interval timer in said computer upon the closure of the press for monitoring the elapsed time of said closure, constantly determining the temperature (Z) of the mold at a location closely adjacent to the mold cavity in the press during molding,

c. constantly providing the computer with the temperature (Z), repetitively calculating in the computer, at frequent intervals during each cure, the Arrhenius equation for reaction time during the cure, which is $\ln v = CZ + x$

d. where v is the total required cure time, repetitively comparing in the computer at said frequent intervals during the cure each said calculation of the total required cure time calculated with the Arrhenius equation and said elapsed time, and

e. opening the press automatically when a said comparison indicates equivalence.

V. Claim 1 of Prometheus

A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug

subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES,
d/b/a MAYO MEDICAL LABORATORIES, ET AL.

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.

Respondent.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF THE INTELLECTUAL PROPERTY LAW ASSOCIATION OF CHICAGO AS *AMICUS CURIAE* SUPPORTING RESPONDENT

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INTEREST OF THE AMICUS[1]

Founded in 1884, the Intellectual Property Law Association of Chicago ("IPLAC") is the oldest intellectual property law association in the nation. Its approximately 1,000 members represent a full spectrum of the profession ranging from law firm attorneys to sole practitioners, corporate attorneys, law school professors, and law students. IPLAC is centered in Chicago, a principal forum for patent litigation in this country. Every year, IPLAC's members prosecute thousands of patent applications and litigate many patent lawsuits.[2]

IPLAC is a not-for-profit organization dedicated to maintaining a high standard of professional ethics in the practice of patent, trademark, copyright, trade secret, and associated fields of law. A principal aim is to aid in the development and administration of these laws and the manner by which they are applied by the courts and by the United States Patent and Trademark Office. IPLAC is further dedicated to providing a medium for the exchange of views on intellectual property law among those

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[1] In accordance with Supreme Court Rule 37.6, IPLAC states that this brief was not authored, in whole or in part, by counsel to a party, and that no monetary contribution to the preparation or submission of this brief was made by any person or entity other than IPLAC or its counsel.

[2] While over 30 federal judges are honorary members of IPLAC, none of them was consulted or participated in any way on this brief.

practicing in the field and to educating the public at large.

IPLAC has no interest in any party to this litigation or stake in the outcome of this case, other than its joint desire for a correct interpretation and application of the United States Patent Laws. In accordance with Supreme Court Rule 37, counsel of record for the parties have filed letters with the Clerk of Court consenting to the filing of amicus briefs.

SUMMARY OF ARGUMENT

The framers of our Constitution understood the importance of rewarding inventors, for limited times, for their creative endeavors. Congress then implemented a plan for protecting the rights of the inventor and promoting the advance of the useful arts by broadly drafting the patent statute without technological exclusions, ready to embrace yet unknown innovations. Thus, the language of 35 U.S.C. § 101 ("section 101") places few limits on the types of invention eligible for patent protection and reflects Congress' judgment on how best to fulfill its Constitutional mandate.

For more than a century, the Court has applied section 101 using a flexible and broad subject matter analysis to accommodate incredible, sweeping, and unforeseen advances in technology. Without such subject matter flexibility, many of the inventions that have made the United States the technology leader of the world would never have been discovered or would have been hidden from the

public with no incentive for revelation or commercialization. Similarly, section 101's flexibility accommodates smaller yet still deserving inventions. It is this elasticity of section 101, with few exceptions and without technological limitation, that has helped to make the U.S. patent system the strongest in the world, supporting innovation like no other.

Yet, Petitioner seeks to have the Court rule on a specific type of claim, indeed a specific claim, and determine whether this category, "correlations between blood test results and patient heath," can exist as patentable subject matter. This is precisely the type of specific exclusion the framers sought to avoid and that Congress through its implementation in statute carried forth. Rather than precluding all uses of a natural phenomenon, Prometheus' claims merely seek to preempt others from using a particular application of that phenomenon, precisely the type of subject matter envisioned to be encompassed by the patent statute.

Petitioners sound the alarm that should this case stand, it will become a beacon for issuance and maintenance of "bad patents." However, such broad hyperbole does not comport with the totality of the requirements for achieving patentability. Section 101 is, by design, a "coarse filter." PTO, *Interim Guidance for Determining Subject Matter Eligibility for Process Claims in View of Bilski v. Kappos*, 75 Fed. Reg. 43,922, 43,926 (July 27, 2010).

After section 101, the remaining provisions of the Patent Act require the nuanced, fact-intensive distinctions necessary to separate patentable from unpatentable inventions. A patentable invention

must be both new and nonobvious. In addition, the inventor must fully and clearly describe the invention to enable others to understand and practice it. The inventor also must claim the invention distinctly to inform the public of its reasonable metes and bounds. Enforcement of these requirements ensures that granted patents legitimately promote the useful arts and advance the frontiers of technology, as the nation's founders intended. The public domain, and Mayo's concerns, therefore, are adequately protected by these other, more stringent, criteria for patentability.

IPLAC urges the Court not to disturb the broad and accessible threshold of statutory subject matter that has fostered innovation and public disclosure over a wide variety of useful arts—and importantly, in new and emerging fields of technology. The judgment of the Federal Circuit should be affirmed.

DISCUSSION

I. The Claimed Method Satisfies Congress' Broad Mandate Under 35 U.S.C. Section 101

A. The Court Has Fulfilled Congress' Intent to Construe Section 101 Broadly

The Federal Circuit's decision is consistent with the Court's precedent over the past half century. Section 101 broadly defines the scope of patent eligible subject matter:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101. Thus, section 101 sets forth four separate categories of statutory subject matter: "*any* new and useful [1] process, [2] machine, [3]manufacture, or [4] composition of matter." *Id.* (emphasis & numbering added). Prometheus' claims at issue cover a specific process, i.e., category [1] above. That process specifies the discovery in patients with immune gastrointestional disorder of a therapeutically effective, non-toxic dose of thioguanine. The claimed process recites specific yields and ranges; it is not vague.

This Court has interpreted the language of section 101 broadly: "In choosing such expansive terms as 'manufacture' and 'composition of matter,' modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope." *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980). Devoid of limiting language, section 101 readily accommodates the rapid pace of innovation and the assimilation of new technologies, including technologies never anticipated at the time section 101 was enacted. As this Court has put it, patentable subject matter includes "anything under the sun that is made by man." *Id.* at 309. Thus, this Court has not seen fit to exclude particular

technologies from section 101, no matter how unusual or bizarre. *See Diamond v. Diehr*, 450 U.S. 175, 182-83 (1981).

Recently the Court in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), confirmed the liberal application of section 101. Considering the Federal Circuit's "machine or transformation" test for determining patentable subject matter, the Court "cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed" and ruled that "machine or transformation" could not be the *sole* test under Section 101. *Id.* at 3226 (quotations omitted). "Congress plainly contemplated that the patent laws would be given wide scope," and "took [a] permissive approach to patent *eligibility* to ensure that ingenuity should receive a liberal encouragement." *Id.* at 3225 (quotations omitted & emphasis added).

Although the Court in *Bilski* recognized that its precedents provide "three specific exceptions" to section 101's patent-eligibility principles, these exceptions do not give "the Judiciary *carte blanche* to impose other limitations that are inconsistent with the text and the statute's purpose and design." *Id.* at 3226. This is yet another opportunity for the Court to reaffirm the broad scope of section 101.[3]

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[3] The Court also has emphasized the importance of the flexible approach to patent law in other contexts outside section 101. *See, e.g., KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 407, 415, 427 (2007) (rejecting rigid interpretation of 35 U.S.C. § 103 imposing "teaching,

(Continued ...)

B. The Asserted Process Claims Recite Patent-Eligible Subject Matter and Do Not "Wholly Preempt" Any Natural Phenomenon

Consistent with the broad language and interpretation of section 101, the Federal Circuit correctly applied this Court's narrow exceptions for laws of nature, physical phenomena, and abstract ideas. This protection of the public commons does not place limits or exclusions on the *subject matter* of the four specified categories of section 101; instead, it provides guidance to the decision-maker to prevent wholesale removal from the public of natural or scientific principles.

The few exceptions that exist to section 101—laws of nature, physical phenomena, and abstract ideas—are a matter of common sense: An inventor is not entitled to claim one of these basic principles in isolation because to do so would remove it from the public. *See, e.g.*, *Diehr*, 450 U.S. at 185.[4] These are

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suggestion, or motivation test (TSM) test" as sole test for obviousness; section 103 "must not be confined within a test or formulation too constrained to serve its purpose" (quotations omitted)); *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 738 (2002) (rejecting "complete bar" test, as an unbending approach to the doctrine of prosecution history estoppel; "we have consistently applied the doctrine in a flexible way, not a rigid one").

[4] *Diehr* described the true limits on patent eligibility:

(Continued ...)

the "basic tools of scientific and technological work," *Gottschalk* v. *Benson*, 409 U.S. 63, 67-68 (1972), "free to all men and reserved exclusively to none," *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) (*Funk Bros.*).

For example, the Court has refused to permit a patent claim only where it would "wholly pre-empt" the use of a mathematical formula. *Benson*, 409 U.S. at 71-72. A mathematical formula, which, "like a law of nature, ... cannot be the subject of a patent." *Diehr*, 450 U.S. at 185-86. "It is now commonplace that an *application of* a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Id.* at 187 (emphasis added); *see also O'Reilly* v. *Morse*, 56 U.S. 62, 119 (1856) (provided application contains sufficient detail, "[w]hoever discovers that a certain useful result will be produced in any art, machine, manufacture, or composition of matter by the use of certain means is entitled to a patent for

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> This Court has undoubtedly recognized limits to § 101 and every discovery is not embraced within the statutory terms. Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas. 'An idea of itself is not patentable. A principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right.'

Id. at 185 (internal citations & quotations omitted).

it"). Thus, "it is equally clear that a process is not unpatentable simply because it contains a law of nature or a mathematical algorithm." *Parker v. Flook*, 437 U.S. 584, 590 (1978).

In *Diehr*, this Court held that a claim that incorporated a mathematical equation constituted patentable subject matter because the claim, as a whole, defined a rubber molding process and not just an equation. 450 U.S. at 192–93. In doing so, the *Diehr* Court distinguished two earlier decision by the Court: *Parker v. Flook* and *Gottschalk v. Benson*. Distinguishing *Flook* as merely reciting a mathematical formula, the Court stated: "In contrast [to *Flook*], the respondents here do not seek to patent a mathematical formula. Instead, they seek patent protection for a process of curing synthetic rubber." *Diehr*, 450 U.S. at 187.[5] "Even though a phenomenon of nature or mathematical formula may be well known, an inventive application of the principle may be patented." *Flook*, 437 U.S. at 594.

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[5] Although the Court concluded that the claims in *Flook* did not entirely pre-empt the mathematical formula at issue, it held that lack of preemption did not necessarily establish eligibility as a process claim. 437 U.S. at 589. There also must be "some other inventive concept in [the] application" of the formula. *Id.* at 594. The problem in *Flook* arose because the claim was not sufficiently definite and lacked specific utility, an issue more appropriately addressed under sections 102, 103 and 112. (*See infra* pp. 14-20.)

Similarly, the claims in *Benson* were directed to a method of programming a computer to convert signals from binary coded decimal form into pure binary form. The Court rejected the claims because they were not limited in scope; indeed, "the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm *itself*." *Benson*, 409 U.S. at 71-72 (emphasis added).

The mathematical formula at issue in *Diehr* was well known, as were the process steps of installing rubber in a press, closing the mold, and determining the temperature of the mold. Additional steps included "constantly recalculating the appropriate cure time through the use of the formula and a digital computer, and automatically opening the press at the proper time." *Diehr*, 450 U.S. at 187. While the Court noted that "insignificant post-solution activity will not transform an unpatentable principle into a patentable process," *id.* at 191-92, that was not the case in *Diehr*:

> On the other hand, when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect (e.g., transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of §101.

Id. at 192. What separates abstract ideas, scientific truths, or phenomena of nature from patent-eligible

invention is the application of the idea, truth or phenomena to "a new and useful end." *Diehr*, 450 U.S. at 188 n.11 (quotations omitted); *see also Mackay Radio & Tel. Co. v. Radio Corp.*, 306 U.S. 86, 94 (1939) ("[w]hile a scientific truth, or the mathematical expression of it, is not patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be." (quotations omitted)).

C. Congress Did Not Intend To Create Different Section 101 Tests For Different Claim Types

Accepting Mayo's arguments in this case would lead to a rule carving out from section 101 certain types of claims—like the diagnostic methods claims at issue—and treating them differently. Indeed, Mayo all but concedes that it is seeking the development of special rules for such claims: its Petition (at 18) asserts that the "appropriate application of Section 101 to biotechnology claims, *and particularly the application of Section to method claims involving natural, biological correlations*, needs resolution." (emphasis added).

This is precisely the approach to section 101 that the Court in *Bilski* rejected. In *Bilski*, two "categorical limitations" on "process" patents under section 101 were proposed: the "machine-or-transformation test" and the categorical exclusion of "business method" patents. 130 S. Ct. at 3225. Neither was adopted by the Court. *See id.* at 3228 ("Section 101 similarly precludes the broad contention that the term 'process' categorically excludes business methods.").

Rigid rules excluding types of subject matter have been rejected. *See, e.g.*, *Quanta Computer, Inc. v. LG Elecs., Inc.*, 128 S. Ct. 2109 (2008) (rejecting rule excluding method claims from the doctrine of patent exhaustion). The unanimous Court in *Quanta Computer* noted, "[o]ur precedents do not differentiate transactions involving embodiments of patented methods or processes from those involving patented apparatuses or materials." *Id.* at 2117; *see also Benson*, 409 U.S. at 67-68 ("We dealt there with a 'product' claim, while the present case deals with a 'process' claim. But we think the same principle [of preemption] applies."). This Court concluded that the patent exhaustion analysis for a process claim depends on the facts of the particular case, just as it does for an apparatus claim. *Quanta Computer*, 128 S. Ct. at 2118. The Court should do the same here—carving out Prometheus' patent claims from section 101 would create a new set of preemption rules for diagnostic methods claims, while the low bar set by the "wholly preempt" rule in *Diehr* would apply to all other patent claims. "[C]ourts must be cautious before adopting changes that disrupt the settled expectations of the inventing community." *Festo*, 535 U.S. at 739. Prometheus' claims fall within the scope of patentable subject matter under section 101.

II. Section 101 Eligibility Is Different Than The Required Analysis Under Sections 102, 103, and 112

A. Satisfying Section 101 Does Not Mean A Patent Will Issue.

Applying the *Diehr* test for patentable subject matter to Prometheus' claims, a first inquiry asks: do

the claims include a mathematical formula, scientific principle, or phenomenon of nature? If, as here, the answer appears to be yes, the second inquiry must be: does the claim, *as a whole*, apply or implement the mathematical formula, scientific principle, or phenomenon of nature in a specific, *useful* process or product? As to the claims at issue, the answer is yes.

More explicitly, claim 1 requires the specific steps of "administering a drug providing 6-thioguanine to a subject," and "determining the level of 6-thioguanine in said subject." See '623 Patent, claim 1, col. 19, ll. 13-16. Those specific steps satisfy a patent-eligible process under Section 101 because the claim requires multiple steps that cause a useful result (treatment of a disorder) by transforming the patient's body chemistry. The "determining" step also can be said to require the transformation of blood or tissue sample on which the metabolite test is performed. See Pet. App. 18a-19a; '623 patent, col. 9, l. 12 to col. 10, l. 14.2.

Mayo's argument that the Court should disregard the "administering" and "determining" steps because those steps are "[w]ell-known" and have been "familiar to physicians for decades," Pet. Br. 36, misunderstands the rubric of Section 101 and its interplay with the other statutory sections. Section 101 itself ends with the foreshadowing caveat that even though a claim may be said to contain patent eligible subject matter, it still must satisfy the other requirements of sections 102, 103, and 112. "The understanding that these three requirements are *separate and distinct* is long standing and has been universally accepted." *In re*

Bergy, 596 F.2d 952, 960 (CCPA 1979) (emphasis in original), *vacated & affirmed by Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

Judge Rich described them as doors that require separate keys. *Id.* at 960-62. In other words, simply because an invention contains patent eligible subject matter does not mean that a patent should issue. "The 'novelty' of any element or steps in a process, or even of the process itself" is a separate question to be considered under § 102 and "is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter." *Diehr*, 450 U.S. at 188-89. Section "101 was never intended to be a 'standard of patentability'; the standards, or conditions as the statute calls them, are in § 102 and § 103." *Bergy*, 596 F.2d at 963; *see also Diehr*, 450 US. at 189 (reinforcing that section 101 is a "general statement of the type of subject matter that is eligible for patent protection" and section 102 "covers in detail the conditions relating to novelty.") (citations omitted).

The legislative history is consistent. "Section 101 sets forth the subject matter that can be patented, 'subject to the conditions and requirements of this title.' The conditions under which a patent may be obtained follow, and section 102 covers the conditions relating to novelty." S. Rep. No. 82-1979, 82d Cong., 2d Sess., at 5 (1952), *reprinted in* 1952 U.S.C.C.A.N. 2399. Once section 101 is satisfied, the inventor still must satisfy sections 102, 103 and 112 before he will be entitled to a patent. *See Bergy*, 596 F.2d at 960-62 (discussing separate doors for sections

102 and 103). The object and purpose of section 103 is to promote "really novel advances in the art, rather than those attributable merely to a person having ordinary skill in the trade." *Vincent v. Suni-Citrus Prods. Co.*, 215 F.2d 305, 315 (5th Cir. 1954). The test of nonobviousness is independent of the tests of novelty and utility, and patentability depends upon satisfaction of all three requirements. *See, e.g., Nat'l Dairy Prods. Corp. v. Borden Co.*, 261 F. Supp. 771 (E.D. Wis. 1966); *see also Eimco Corp. v. Peterson Filters & Eng'g Co.*, 406 F.2d 431 (10th Cir. 1968); *Bros. Inc. v. Browning Mfg. Co.*, 317 F.2d 413 (8th Cir. 1963).

Critics of a broad reading of section 101 express concern that if the scope of patentable subject matter is not cabined, innovation will be reduced.[6] However, these arguments disregard the other sections of the patent statute—the other doors

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[6] *See, e.g.*, Robert M. Kunstadt, *Sneak Attack on U.S. Inventiveness*, NAT'L L.J., Nov. 9, 1998 (complaining in the wake of the Federal Circuit's decision in *State Street Bank & Trust Co. v. Signature Financial Group, 149 F.3d 1368 (Fed. Cir. 1998)*, "It will be impossible to operate such businesses [advertising and marketing agencies] without advice from patent counsel."); *but see*, William J. Simmons, *Bilski Blundering Biotech*, NATURE BIOTECHNOLOGY, March 2009, at 245 (complaining in the wake of the *Bilski* Federal Circuit decision that, "A recent change in the law, ... applies to pharma and biotech subject matter and may have a dramatic impact on the procurement and enforcement of patent rights in the U.S.").

in Judge Rich's analysis that must be unlocked before a patent may issue. *See Bergy*, 596 F.2d at 960.

The profound truth underlying Congress' broad statement of eligibility is that it fosters *more* innovation. Indeed, the foundation of our patent system is the notion that the lure of a United States patent encourages creativity.[7] Filing an application provides the applicant's *quid pro quo*—disclosure and ultimate publication—to the benefit of the public. Even if those applications do not issue as patents, the public benefits because of their dedication. A cramped reading of section 101 would discourage filings, and we would never know what the public lost without them.

Recognizing that section 101 opens only that first door to examination provides a lead toward resolving this Court's questions. The applicant still must open three more doors to sections 102, 103 and 112. *See, e.g., SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1342, 1346 (Fed. Cir. 2005)

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[7] *See, e.g., The Supreme Court Engages in Judicial Activism in Interpreting the Patent Law in eBay, Inc. v. MercExchange, L.L.C*, 10 Tul. J. Tech. & Intell. Prop. 165, 199-200 (2007) (a strong patent system provides incentives for enterprises and capital to smaller enterprises; however, a weaker patent system allows existing dominant enterprises to avoid additional competition and by reducing the economic value of patents increases incentives for the dominant enterprises to infringe).

(concluding that the claim at issue was directed to eligible subject matter under section 101, but holding the claim anticipated under section 102).

B. The Court Previously Has Recognized that Section 101 Is A Gateway To Further Inquiry.

The above approach also is compatible with the concerns Justice Breyer expressed in *Laboratory Corporation of American Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) (Breyer, J., dissenting from dismissal for improvidently granted review) about the dangers to innovation of too many patents. The issue is not the legitimacy of that danger but about which door to leave open to affect the necessary control. In this case and in others, the appropriate doors to substantively monitor are found in the "conditions for patentability," i.e., where the claims are examined under sections 102, 103 and 112, not in the scope of subject matter eligible for patentability generally under section 101.

Indeed, this Court's analysis of the issue in *O'Reilly v. Morse* more closely tracks the language of today's section 112 rather than section 101. *Morse*, 56 U.S. 62, 112-13 (1856). In *Morse*, the court held that "[w]e perceive no well-founded objection to the description which is given of the whole invention and its separate parts, nor to his right to patent for the first seven inventions set forth in the specification of his claims. The difficulty arises on the eighth." 56 U.S. at 112 (emphasis added). The Court held that the rejected patent claim (no. 8) was too broad:

> [H]e claims an exclusive right to use a manner and process which he has not

> described and indeed had not invented, and therefore could not *describe* when he obtained his patent. The court is of opinion that the claim is too broad, and not warranted by law.

Id. at 113 (emphasis added). This Court went on to explain that if the patentee "specifies the means he uses in a manner so full and exact that anyone skilled in the science to which it appertains can, by using the means he specifies, without any addition to or subtraction from them, produce precisely the result he describes, ... the patent confers on him the exclusive right to use the means he specifies to produce the result or effect he describes, and nothing more." *Id.* at 119 ("And if this cannot be done by the means he describes, the patent is void.").

Similarly, Mayo's complaint here is not about statutory subject matter, but about the scope of the claims compared with the underlying description of the invention. For instance, Mayo's Brief asserts that "Prometheus' claims do not recite any amount of any drug to be given to any patient." Mayo also asserts that the claims at issue "say nothing about the ultimate use of the correlations, and thus cover all types of treatment, research, or any other kind of activity. Pet. App. 25. In short, Mayo's complaints are over the language of Prometheus' claims, *not* whether it satisfies patentable subject matter.[8]

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[8] "Patent drafters know how to recite administration of a therapeutically effective amount of a (Continued ...)

To the extent that Mayo's concerns may be legitimate, they should be properly addressed under one of the substantive statutory sections. In this case, the appropriate door under Judge Rich's analysis is found in the "conditions for patentability," i.e., sections 102, 103 and 112, not in the scope of subject matter under section 101, which would risk foreclosing valuable and unforeseeable future innovations.

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drug for method of treatment claims. Prometheus was careful not to do so here. (Pet. 25-26 (internal citations and quotations omitted) (alleging that Prometheus' claims employed "drafting tricks" to remove "huge swaths of basic medical knowledge").)

CONCLUSION

For the foregoing reasons, IPLAC respectfully request that the Court affirm the judgment of the Federal Circuit.

Respectfully submitted,

NOVEMBER 7, 2011

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES, DBA MAYO MEDICAL LABORATORIES, et al.,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.

Respondent.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF *AMICUS CURIAE* INTELLECTUAL PROPERTY OWNERS ASSOCIATION IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICUS CURIAE*[1]

Amicus curiae Intellectual Property Owners Association (IPO) is a trade association representing companies and individuals in all industries and fields of technology who own or are interested in intellectual property rights. IPO's membership includes more than 200 companies and a total of over 12,000 individuals who are involved in the association either through their companies or as inventor, author, executive, law firm, or attorney members. Founded in 1972, IPO represents the interests of all owners of intellectual property. IPO regularly represents the interests of its members before Congress and the USPTO and has filed *amicus curiae* briefs in this Court and other courts

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[1] No counsel for a party authored this brief in whole or in part, and no such counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than the *amicus curiae* or its counsel made a monetary contribution to its preparation or submission. The parties have consented to the filing of this brief by blanket consent letters filed with the Court on August 4 and 8, 2011.

on significant issues of intellectual property law. The members of IPO's Board of Directors, which approved the filing of this brief, are listed in the appendix.[2]

INTRODUCTION

Consistent with the goal of "promot[ing] the Progress of Science and useful Arts," set forth in Article I, Section 8, Clause 8 of the U.S. Constitution, Congress and Courts alike have broadly defined the types of inventions that may be eligible for patent protection. This goal of promoting innovation, which is served by a broad interpretation of "process, machine, manufacture, or composition of matter," within the meaning of 35 U.S.C. § 101, must be considered in light of concerns that the patenting of mere ideas, or natural laws or phenomena, will preempt all uses of those ideas, natural laws or phenomena, thus stifling innovation. To balance these important concerns, courts uniformly exclude certain fundamental building blocks of invention

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[2] IPO procedures require approval of positions in briefs by a three-fourths majority of directors present and voting.

(*i.e.*, natural phenomena, laws of nature, and abstract ideas) from the scope of patentable subject matter. The present case requires consideration of the boundary, in the field of medicine, between a non-patent-eligible natural phenomenon, and a specific, practical, and patent-eligible application of that natural phenomenon.

SUMMARY OF ARGUMENT

This Court has long recognized the need for patent law to incentivize innovation and the public disclosure of such innovation. This need is particularly crucial in the field of medicine, given the potential life-changing importance of its breakthroughs and the rapid pace of discoveries in the industry. This Court's precedent appropriately acknowledges that in 35 U.S.C. §101 a broad scope of patent-eligible subject matter well serves this goal. Although there is some concern that such a broad scope may in rare instances result in allowance of exclusive rights that may prove undesirable, the prevention of undesirable instances is more appropriately addressed with other substantive requirements for patentability.

In this case, the U.S. Court of Appeals for the Federal Circuit construed the asserted claims as methods of treatment, requiring a specific application of a correlation of metabolites in the body that requires a transformation of matter to a different state. The Federal Circuit held that the asserted claims represent patent-eligible subject matter under 35 U.S.C. § 101. Under this Court's precedent, such methods of treatment are patent eligible subject matter. Respondent's arguments to the contrary should be rejected, for they seek to draft new, extra-statutory exceptions onto Section 101 of the Patent Act or confuse patent-eligibility under Section 101 with the conditions for patentability under Sections 102, 103 and 112. IPO therefore urges this Court to affirm the judgment of the Federal Circuit.

ARGUMENT

I. Section 101 is a Low Threshold for Patent-Eligible Subject Matter, And Should Not Be Merged With the More Stringent Patentability Requirements of Novelty, Non-Obviousness,

Enablement and Sufficient Written Description.

This Court has referred to the assessment of the patentability of an invention under Section 101 as a "threshold" inquiry. *Diamond v. Diehr*, 450 U.S. 175, 188 (1981); *Bilski v. Kappos*, 130 S.Ct. 3218, 3225 (2010). This inquiry is separate from assessing whether a patent claim meets the substantive conditions for patentability set forth elsewhere in the Patent Act. *Id.; Parker v. Flook*, 437 U.S. 584, n.18 (1978). This Court has appropriately held that permissive application of this "threshold" is consistent with Congressional intent, as evidenced by the statutory language and legislative history. *See Diamond v. Chakrabarty*, 447 U.S. 303, 307-08 (1980).

In this case, the Petitioners appear to be asking this Court to use Section 101 beyond its intended purpose as a permissive threshold for filtering patent-eligible subject matter. Repeatedly, Petitioners' Brief suggests that the claimed invention should not be patentable because it involves methods that are well-known to doctors, thereby implicating

issues of novelty or obviousness. *See* Brief For Petitioners ("Pet. Br.") at 22, 24-25, and 34-35.

As this Court recognized in *Diehr* and *Flook*, courts should not confuse the issue of patentability under Section 101 with the analysis of novelty or obviousness under Sections 102 and 103, respectively. *Diehr*, 450 U.S. at 189-90; *Flook*, 437 U.S. at n.18. "The question therefore of whether a particular invention is novel is 'wholly apart from whether the invention falls into a category of statutory subject matter.'" *Diehr*, 450 U.S. at 190 (quoting *In re Bergy*, 596 F.2d 952, 961 (C.C.P.A. 1979)). This Court has explicitly rejected Petitioners' approach "to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis," finding that approach particularly inappropriate for process claims, which may be patentable "even where all the constituents of the combination were well known and in common use before the combination was made." *Diehr*, 450 U.S. at 188.

The other requirements for patentability—novelty under Section 102, non-obviousness under

Section 103, and written description and enablement under Section 112—are more appropriate gatekeepers for determining the patentability of inventions. Section 101 merely defines the field of patent-eligible subject matter. The substantive requirements for patentability provide strong protection against overreaching claims that seek exclusive rights on pre-existing knowledge. Under Sections 102 and 103 of the Patent Act, an inventor is already prohibited from patenting an application of a phenomena of nature that is not novel or non-obvious. Similarly, under Section 112, an inventor is entitled to protection only to the extent that his inventions are fully described in and enabled by the disclosure that he provides.

Accordingly, even if there is some concern over whether the particular claims at issue in this case should be patentable in view of the "well-known" subject matter that they encompass (Pet. Br. at 24-25), the Court should not accept Petitioners' invitation to narrow the scope of patent-eligible subject matter under Section 101 in order to

invalidate the claims.[3] Rather, the Court should apply Section 101 in its proper purpose as a permissive threshold, and leave for another day the questions of whether the substantive conditions of patentability are met for the claimed invention.

II. A Broad Scope of Subject Matter Eligibility is Particularly Important for Medical Treatments.

This Court has repeatedly recognized that a permissive approach to subject matter eligibility serves an important role in promoting technological innovation in our country. *E.g.*, *Bilski*, 130 S.Ct. at 3225; *Chakrabarty*, 447 U.S. at 308. This Court also has acknowledged that this approach is consistent with the intent of our country's founders and Congress: "Congress took [a] permissive approach to patent eligibility to ensure that 'ingenuity should receive a liberal encouragement.'" *Chakrabarty*, 447 U.S. at 308 (quoting 5 Writings of Thomas Jefferson 75-76 (Washington ed. 1871)). In accordance with

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[3] IPO takes no position on whether Respondent's claims meet these other requirements for patentability.

this intent, "anything under the sun that is made by man" falls within the scope of patent-eligible subject matter. *Chakrabarty*, 447 U.S. at 308-09.

With these goals in mind, this Court has "more than once cautioned that courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed.'" *Bilski*, 130 S.Ct. at 3226 (quoting *Diehr*, 450 U.S. at 182). Likewise, the Court has emphasized the need for flexibility in the law to accommodate technological innovation: "Section 101 is a 'dynamic provision designed to encompass new and unforeseen inventions.'" *Bilski*, 130 S.Ct. at 3227 (quoting *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 135 (2001)).

The incentive that patent protection creates is particularly important with the rapid pace and unpredictability of medical treatments. The field of diagnostic medicine continues to develop, and scientists increasingly have been able to diagnose, predict, and treat medical conditions that were not long-ago unknown. For example, the promise of patent protection has led to the development of high-profile innovations like a prognosis for colon cancer

(U.S. Patent No. 7,163,801), a test for HIV/AIDS (U.S. Patent No. RE 38,352), and a test for breast and ovarian cancer (the HER-2/neu test, U.S. Patent No. 4,968,603). These medical advances depend heavily on the strong protection of intellectual property rights.

Patent protection for medical innovations has jump-started growth in the biotechnology industry, especially in small-to-mid size companies that rely heavily on patented technologies. *See NIH: Moving Research from the Bench to the Bedside: Hearing Before the Subcomm. On Health of the H. Comm. On Energy and Commerce*, 108th Cong. 47 (2003), *available at* http://energycommerce.house.gov/108/action/108-38.pdf (detailing the development of small biotechnology companies, and the research and development costs needed to sustain them). Developing a discovered correlation into a marketable diagnostic technology is extremely costly, and requires the efforts of venture capitalists, developers, managers, laborers, technologists, manufacturers, marketers, and distributors. *See* F. Scott Kieff, *On the Importance to Economic Success*

of Property Rights in Finance and Innovation, Searle Center Annual Review of Regulation, May 4, 2007, at 4-5, *available at* www.law.northwestern.edu/searlecenter/papers/Kieff_Annual_Rev_Final.pdf. Patent protection encourages this diverse group of people to cooperate. As in other fields, the eligibility for patent protection for medical treatment methods creates the incentive for inventors to disclose the innovation to the public in exchange for such protection. Correspondingly, the profit potential that may flow from the exclusive rights of an enforceable patent covering a medical invention provides the incentive for parties to work together to bring an innovation to market. *Id.* at 5. If the patent eligibility of medical diagnostic tools is questioned—or eliminated—funding for risky and expensive projects will be less forthcoming, and in turn, advances in medical diagnostic testing will be less forthcoming as well.

A change in the broad application of Section 101 not only would upset settled expectations in the medical field, but it could have a destructive impact on the continued advances in medicine that have led to society-improving breakthroughs. Only if

scientists, doctors, and investors can rely on broad access to patent protection will we continue to benefit from the incredible innovation in this field that our society has enjoyed in the last several decades.

III. Transformative Methods of Medical Treatment and Diagnostics Should be Patentable.

Although the line is not a bright one that makes the patent-eligibility of an invention a simple assessment, this Court has consistently recognized three categories that fail to meet the threshold for patent-eligibility subject matter under Section 101: laws of nature, natural phenomena, and abstract ideas. *E.g., Diehr*, 450 U.S. at 185. On the other hand, this Court's precedent recognizes that *applications* of laws of nature, natural phenomena, and abstract ideas, which are new productions from these elements, are patent-eligible. *See Parker v. Flook*, 437 U.S. 584, 591 (1978) ("While a scientific truth, or the mathematical expression of it, is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be.") (quoting *Mackay Radio & Telegraph Co. v. Radio Corp. of America*, 306 U.S. 86, 94 (1939)).

Transformative methods of treatment should be patent-eligible. In the context of a specific category of disease, a novel method for the application of a naturally-occurring correlation with treatment steps that involve transformations of the body is eligible for patent protection. This Court indicated in *Gottschalk v. Benson* that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." 409 U.S. 63, 70 (1971). Although the Court has since clarified that the machine-or-transformation test is not the sole criterion on which patent eligibility determinations should be based, the Court continues to recognize that transformation is an important investigative clue "for determining whether some claimed inventions are processes under § 101." *Bilski,* 130 S. Ct. at 3227. And while the Court was previously addressing transformations in the context of programming a binary computer (as in *Gottschalk*) and hedging investment losses (as in *Bilski*), methods of medical treatment that involve changes in the human body are no different. In fact, for the

reasons explained in Section II above, this type of process may be more deserving of broad patent eligibility than other fields of science and technology.

In this case, the Federal Circuit made it clear that it was interpreting the claims as active methods of treatment for a specific disease. *Prometheus Labs, Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1355-56 (Fed. Cir. 2010). The Federal Circuit found that: "[t]he claims recite specific treatment steps, not just the correlations themselves. And the steps involve a particular application of the natural correlations: the treatment of a specific disease by administering specific drugs and measuring specific metabolites." *Id.* at 1355. The Federal Circuit also interpreted the step of "determining the level" (which is present in some form in every asserted claim) as the act of assessing the levels of certain metabolites, not as they are naturally occurring within the body of the subject, but rather, as affected by one or more drugs that have been administered to the subject. *Id.* at 1350-51. Although the Petitioners challenge whether the patent claims at issue contain patentable subject matter, they do not appear to

challenge the Federal Circuit's interpretation of these claims.[4]

Accordingly, the unchallenged construction of these claims requires a transformation of certain metabolites in the body in the treatment of a specific category of disease. As such, under this Court's precedent, the claims are directed to a patent-eligible specific application of a natural phenomenon.

This Court should also decline Petitioners' suggestion to separately analyze, as part of a Section 101 analysis, whether certain parts of Respondent's claims are merely data-gathering or insignificant post-solution activity. Such an inquiry impermissibly slices up the claim into various components, a tactic that this Court previously rejected in assessing the patentability of an invention. *Diehr,* 450 U.S. at n.12 (rejecting the

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[4] The IPO takes no position on whether or not Respondent's patent claims were properly interpreted. Rather, the opinions expressed in this *Amicus* Brief simply start with the presumption that the claims have been properly interpreted as transformative methods of treatment.

request to "dissect[] a claim into old and new elements" when assessing patentable subject matter "because all inventions can be reduced to underlying principles of nature which, once known, make their implementation obvious"). As explained in *Diehr*, when a claim applies a formula "in a structure or process which, *when considered as a whole*, is performing a function which the patent laws were designed to protect (*e.g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101." 450 U.S. at 192 (emphasis added).

Like the claims considered by the Court in *Diehr*, methods for treatment of a specific disease, that require transformation of bodily components based on administration of a drug, do not pre-empt all uses of any natural correlations or mathematical formulas. Thus, Respondent's claims are directed to a "process," which Congress in 35 U.S.C. §101 and this Court in the cases discussed above have defined as a type of invention that may be eligible for patent protection.

CONCLUSION

IPO believes that this Court's precedent appropriately interprets the broad standards for patent-eligible subject matter set forth in Section 101 of the Patent Act. The Court should decline to use this case to erect further, extra-statutory barriers to patent-eligible subject matter that would disrupt those standards, particularly in the field of medical diagnostic techniques, where innovation relies on broad patent protection. The construed claims in this case recite transformative methods of medical treatment that should fall within the broad scope of patent-eligible subject matter.

RESPECTFULLY SUBMITTED,

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1. IPO procedures require approval of positions in briefs by a three-fourths majority of directors present and voting.

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AMICUS CURIAE BRIEF

No. 10-1150

In The
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES,
DBA MAYO MEDICAL LABORATORIES, ET AL.,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF THE JUHASZ LAW FIRM, P.C. AS AMICUS CURIAE SUPPORTING PROMETHEUS LABORATORIES, INC.

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QUESTION PRESENTED

Whether 35 U.S.C. §101 is satisfied by a patent claim that covers observed correlations between blood test results and patient health, so that the claim effectively preempts all uses of the naturally occurring correlations, simply because well-known methods used to administer prescription drugs and test blood may involve "transformations" of body chemistry.

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BRIEF OF THE JUHASZ LAW FIRM, P.C. AS AMICUS CURIAE SUPPORTING PROMETHEUS LABORATORIES, INC.

INTEREST OF AMICUS CURIAE[1]

The authors of this brief are registered patent practitioners with law and science degrees and are members of the patent firm The Juhasz Law Firm, P.C. Paul R. Juhasz has been practicing for 28 years and holds a B.S.Chem.E., a B.S.E.E., a J.D., and a P.E. Chris Frerking has been practicing for 13 years and holds B.S. and M.S. degrees in Computer Science, as well as a J.D. and an LL.M. Both Paul R. Juhasz and Chris Frerking deal with the issue of subject matter patentability for their clients on a regular basis. Mr. Juhasz has written extensively and is extensively published on the Supreme Court's *Bilski* decision and subject matter patentability under 35 U.S.C. §101. They file this brief solely on behalf of the Firm and not on behalf of clients of the Firm. Amicus represent neither party in this action, and offer the following views based on their extensive experience on this matter.

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[1] Pursuant to Sup. Ct. R. 37.6, amicus notes that no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than amicus curiae made a monetary contribution to its preparation or submission. Petitioners and Respondent have consented to the filing of this brief through blanket consent letters filed with the Clerk's Office. A courtesy notice of this filing was provided to both Petitioners and Respondent.

SUMMARY OF ARGUMENT

The court of appeals correctly held that respondent's patent claims are directed to patent-eligible subject matter.

I. For purposes of determining subject matter patentability under 35 U.S.C. §101, the claims in the *Prometheus* diagnostic method patents must be looked at "as a whole" as is done in chemical, mechanical, and electrical patents.

II. The "administering" and "determining" steps in the *Prometheus* claims are not token extra-solution activity but are transformations central to the claim, important to the subject matter patent eligibility determination.

III. The clue to patentability should lie in whether steps that are central to the claim (i.e., not token extra-solution activity) have a "physical" or "virtual" link to a specific physical or tangible object. The *Prometheus* claims have both a "physical" and a "virtual" link and so should be subject matter patentable under 35 U.S.C. §101.

ARGUMENT

I. For purposes of determining subject matter patentability under 35 U.S.C. §101, the claims in the *Prometheus* diagnostic method patents must be looked at "as a whole" as is done in chemical, mechanical, and electrical patents.

This Certiorari was granted on the following question: "Whether 35 U.S.C. §101 is satisfied by a patent claim that covers observed correlations between blood test results and patient health, so that the claim effectively preempts all uses of the naturally occurring correlations, simply because well-known methods used to administer prescription drugs and test blood may involve 'transformations' of body chemistry."

This question is framed in a manner that singles out the "observed correlation" step in the claim as the only step that should be considered in determining whether the claim satisfies 35 U.S.C. §101, since the other steps are characterized as being "well known." While the other steps may or may not be well known, this has no effect on whether 35 U.S.C. §101 is satisfied (though it may be relevant to inquiries under 35 U.S.C. §102 and 35 U.S.C. §103).[2] To determine

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[2] While the diagnostic methodology for working up a body chemistry to enable the observation of a correlation recited in the *Prometheus* claims may ultimately be invalid under 35 U.S.C. §102 and/or §103, that is not the question currently before the Court. The question before the Court concerns only whether the claims are directed to subject matter that is eligible to be patented under 35 U.S.C. §101.

whether 35 U.S.C. §101 is satisfied, it is necessary to consider the claim as a whole. *Diamond v. Diehr*, 450 U.S. 175, 188 (1981).

> "In determining the eligibility of respondents' claimed process for patent protection under §101, their claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis. This is particularly true in a process claim, because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made." *Ibid.*

Thus, the appropriate inquiry is whether the claim as a whole, including all of its steps, preempts all uses of a natural phenomenon, abstract idea, or law of nature. ("Claims that are close to 'laws of nature, natural phenomena, and abstract ideas,' *Diamond v Diehr*, 450 U.S. 175, 185 (1981), do not count as 'processes' under §101, even if they can be colloquially described as such." *Bilski v. Kappos*, 130 S. Ct. 3218, 3238-3239 (2010) (concurring opinion).)

Under this Court's precedent, the transformative steps of "administering" and "determining" in the diagnostic method claims before this Court should be considered in deciding the subject matter patentability question under 35 U.S.C. §101, even if those transformative steps are well-known in the art. Further, the "well-known" transformative steps in the present

case are not unlike transformative steps this Court has routinely addressed and has not excluded from the claim in its subject matter patent eligibility discussion in chemical, mechanical, and electrical patent cases.

The Federal Circuit characterized claims 1 and 46 of U.S. Pat. No. 6,355,623 ("the '623 patent") as representative of the claims at issue in the present case. Claim 1 recites:

> 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Claim 46 is similar, except that it dispenses with the "administering" step and claims only the step of "determining" 6-TG or 6-MMP levels "in a subject

administered a [thiopurine] drug * * * , said subject having said immune-mediated gastrointestinal disorder." '623 patent, col. 23, l. 42 to col. 24, l. 18 *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, 2010 U.S. App. LEXIS 25956, *, 628 F.3d 1347, 97 U.S.P.Q.2D (BNA) 1097 (Fed. Cir. 2010), *cert. granted*, ___ S. Ct. ___, 2011 WL 973139 (June 20, 2011).

The diagnostic step of "administering a drug [to a human body]" in *Prometheus* is not unlike the step of "adding a chemical A to a chemical B" in a chemical process, which is a conventional recitation in the claims of chemical process patents. In this example, the "drug" is to "chemical A" as the "human body" is to "chemical B." Similarly, the step of "determining the level of [the drug's metabolite in the body]" is not unlike "determining the level of (*e.g.*) acidity of a solution," which is another conventional recitation in the claims of many granted and enforced chemical process patents. When viewed in this way, as appears was done below by the Federal Circuit in *Prometheus*, the diagnostic method claims at issue arguably become no different than subject matter that has routinely been seen as patent eligible in chemical process claims.

For example, the subject matter patentability of chemical process patents is evident in *Cochrane v. Badishe*, 111 U.S. 293 (1884), involving a reissued

patent on a product-by-process claim.[3] Although not before the Court in *Cochrane*, the issue of subject matter patentability of the process claim was obliquely addressed by the Court when the Court explained that "another view of the case" is that patentability of the claim lies in the *process* for making the product and not in the product. *Id.*, at 311. The claim in the reissued patent recited: "artificial alizarine, produced from anthracene or its derivatives, by either of the methods herein described, or by any other method which will produce a like result." *Id.*, at 293. Steps very familiar to chemical practitioners such as "adding one part chemical A to one part chemical B," "heating," "obtaining a chemical C," "distilling," "cooling" were not excluded from the claim by the Court in its subject matter patent eligibility discussion. See, Reissue 4,320, Col. 1, para. 2, for example.

In *Tilghman v. Proctor*, 102 U.S. 707 (1880), the chemical process claim recited generally: "the manufacturing of fat acids and glycerin from fatty bodies by the action of water at a high temperature and pressure." *Id.*, at 709. Steps also very familiar to chemical practitioners such as "manufacturing chemical A and chemical B from chemical C," "by the action of water,"

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[3] The patent reissued from U.S. Pat. No. 95,465 which was surrendered and actually reissued in two parts, one for a process for the production of artificial alizarine (RE 4,320) and the other for artificial alizarine produced by either of the methods described in the patent or by any other method producing a like result (RE 4,321). Only the reissued product-by-process claim recited in RE 4,321 was before the Court.

"at a high temperature and pressure," also were not excluded by the Court as to subject matter patent eligibility.

Both product and process claims were before the Supreme Court in *American Fruit Growers v. Brogdex Co.*, 283 U.S. 1 (1931). The Court held the product claims to be not patentable subject matter but set aside the process claims as anticipated. *Id.*, at 14. The process claim recited:

> "3. In the preparation of fresh fruit for market, the process which comprises subjecting fruit to the action of an aqueous solution of borax, the fluidity, strength and temperature of the treating solution, and the duration of the treatment, being such that exposed rind or skin tissues of the fruit are effectively impregnated with borax and rendered resistant to blue mold decay, while at the same time the fruit is not scalded nor is its freshness or edibility otherwise substantially impaired."

Id., at 6. Steps very familiar to chemical practitioners such as "subjecting product A to the action of a solution B," "the fluidity, strength and temperature of solution B being such that. . . ." were not excluded by the Court as to subject matter patent eligibility. Rather, the Court held those process claims to be anticipated – an inquiry that need only be made when the claims are patentable subject matter.

Although *Cochrane*, *Tilghman*, and *American Fruit Growers* were decided before the enactment of 35 U.S.C. §101, this makes no difference to the

analysis. Similar claims are routinely considered to be patent eligible under 35 U.S.C. §101, as the Court in *Diehr*, *supra*, at 175, recognized when embracing *Tilghman* in its 35 U.S.C. §101 analysis.

In finding that a physical and chemical process for molding precision synthetic rubber products falls within the Section 101 categories of patentable subject matter, the *Diehr* Court relied on *Tilghman v. Proctor*, a case involving the original patent Charles Goodyear received on his process for "vulcanizing" or curing rubber, where it was explained that:

> "A manufacturing process is clearly an art within the meaning of the law. Goodyear's patent was for a process, namely, the process of vulcanizing india rubber by subjecting it to a high degree of heat when mixed with sulphur and a mineral salt." *Diehr*, *supra*, at footnote 8.

The *Diehr* Court further relied on *Corning v. Burden*, 56 U.S. 252, 267-268 (1853), where it was explained that:

> "The term machine includes every mechanical device or combination of mechanical powers and devices to perform some function and produce a certain effect or result. *But where the result or effect is produced by chemical action, by the operation or application of some element or power of nature, or of one substance to another, such modes, methods, or operations are called processes.* A new process is usually the result of discovery;

a machine, of invention. The arts of tanning, dyeing, making waterproof cloth, vulcanizing India rubber, smelting ores, and numerous others are usually carried on by processes, as distinguished from machines. One may discover a new and useful *improvement in the process of tanning, dyeing*, &c., irrespective of any particular form of machinery or mechanical device. And another may invent a labor-saving machine by which this operation or process may be performed, and each may be entitled to his patent. *As, for instance, A has discovered that, by exposing India rubber to a certain degree of heat, in mixture or connection with certain metallic salts, he can produce a valuable product, or manufacture; he is entitled to a patent for his discovery*, as a process or improvement in the art, irrespective of any machine or mechanical device. B, on the contrary, may invent a new furnace or stove, or steam apparatus, by which this process may be carried on with much saving of labor and expense of fuel, and he will be entitled to a patent for his machine as an improvement in the art. Yet A could not have a patent for a machine, or B for a process; but each would have a patent for the means or method of producing a certain result, or effect, and not for the result or effect produced. It is for the discovery or invention of some practical method or means of producing a beneficial result or effect that a patent is granted, and not for the result or effect itself. It is when the term process is used to represent the means or method of producing

> a result that it is patentable, and it will include all methods or means which are not affected by mechanism or mechanical combinations." (*emphasis added*) *Diehr*, *supra*, at footnote 7.

So even in *Diehr*, one of the trilogy of cases that along with the definition of §100(b) the *Bilski* Court points to for guidance on what constitutes patentable subject matter, *Bilski*, *supra*, at 3231, the Court recognized the subject matter patentability of transformative chemical processes based on process steps very familiar to chemical practitioners like "subjecting composition A to a high temperature," and "mixing a composition A with a composition B and a composition C," as in the Goodyear patent for making rubber.

Thus, the issue in *Prometheus* is not simply about an "observed correlation," as the question presented strongly suggests. Rather, it is also about a methodology including chemical transformative steps for working up a chemistry inside of the body (to enable the observation of a correlation) not unlike transformative steps that work up a chemistry outside of the body which are not excluded by the Court as to subject matter patent eligibility in chemical process patents. The fact that the "observed correlation" is occurring on body chemistry should be of no consequence. Under this Court's "claim as a whole" precedent, the transformative steps of "administering" and "determining" for working up a body chemistry to enable the observation of a correlation in a diagnostic method patent should be considered no differently

than transformative steps in chemical, mechanical, and electrical process patents.

As this Court stated in *Gottschalk v. Benson*, 409 U.S. 63 (1972): "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Id.*, at 70. Just as the clue to the patentability of a chemical process patent is a chemical transformation, so too one clue to the patentability of diagnostic method claims involving a chemical transformation central to the claim should be a "transformation." The Court's precedent in connection with transformations recited in mechanical and electrical patents further support such a conclusion.[4]

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[4] Similarly, just as the clue to the patentability of a mechanical process and electrical process patent involving a transformation would appear to be a mechanical or electrical transformation, so too one clue to the patentability of diagnostic method claims involving a transformation central to the claim should be a "transformation." See, for example, ***Expanded Metal Co. v. Bradford***, 214 U.S. 366 (1909), where transformation steps very familiar to mechanical practitioners such as simultaneous "slitting and bending," and alternate "slitting and bending" were not excluded as to subject matter patent eligibility. *Id.*, at 377. In ***Smith v. Snow***, 294 U.S. 1 (1935), transformation steps very familiar to mechanical practitioners, such as "arranging [things in an order]" and "applying a current of heated air" were not excluded in its subject matter patent eligibility discussion. *Id.*, at 7-8. In ***The Telephone Cases***, 126 U.S. 1 (1888), steps very familiar to electrical practitioners such as "producing [undulations]," "transmitting [vocal or other sounds]," and "causing electrical [undulations]" were not excluded as to subject matter patent eligibility. *Id.*, at 13-14.

This is not to say that every transformative step is "central," thereby making any diagnostic method claim into patentable subject matter. As this Court has held, token extra-solution activity will not transform an otherwise unpatentable claim into patentable subject matter under 35 U.S.C. §101. *Diehr*, *supra*, at footnote 14.

The "administering" and "determining" steps and their "central-ness" or "insignificance" to the claim must be considered in deciding the subject matter patentability question under this Court's "claim as a whole" precedent and this Court's treatment of transformative steps in chemical, mechanical, and electrical patents.

II. The "administering" and "determining" steps in the *Prometheus* claims are not token extra-solution activity but are transformations central to the claim, important to the subject matter patent eligibility determination.

Just because a method claim involves a transformative step (i.e., a step that performs a transformation) does not mean that the method claim is automatically subject matter patentable. As this Court stated in *Benson*: [t]ransformation and reduction of an article "to a different state or thing" is the *clue* to the patentability of a process claim that does not include particular machines. *Benson*, *supra*, at 70 (*emphasis added*). In the case of a method claim including a transformative step, the transformation is thus an

important indicator that the subject matter may be patentable. The mere existence of the transformation in the claim, however, does not make the claim subject matter patentable *per se*. For guidance on what makes a "process" claim subject matter patentable, the *Bilski* Court pointed to the definition of the term "process" in 35 U.S.C. §100(b) and the *Benson*, *Flook*, and *Diehr* precedent. *Bilski*, *supra*, at 3231.

Unlike the algorithm in *Benson*, the mathematical formula used for monitoring conditions during the catalytic conversion process in the petrochemical and oil-refining industries in *Parker v. Flook*, 437 U.S. 584 (1978) was limited so that it could still be freely used outside the petrochemical and oil-refining industries. *Id.*, at 589, 590. Nevertheless, the *Flook* Court rejected "[t]he notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process."

> "The notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process exalts form over substance. A competent draftsman could attach some form of post-solution activity to almost any mathematical formula; the Pythagorean theorem would not have been patentable, or partially patentable, because a patent application contained a final step indicating that the formula, when solved, could be usefully applied to existing surveying techniques. [Footnote 11] The concept of patentable subject matter under §101 is not 'like a nose of

> wax, which may be turned and twisted in any direction. . . .' *White v. Dunbar*, 119 U.S. 47, 119 U.S. 51."

Id., at 590.

As the Court later stated in *Diehr*, *Flook* stands for the proposition that the prohibition against patenting abstract ideas "cannot be circumvented by attempting to limit the use of the formula to a particular technological environment" or adding "insignificant post solution activity." See *Diehr*, *supra*, at 191-192. Significantly, the Court noted that "[w]e were careful to note in *Flook* that the patent application in *Flook* did not purport to explain how the variables used in the formula were to be selected, nor did the application contain any disclosure relating to chemical processes at work or the means of setting off an alarm or adjusting the alarm limit. *Ibid.* All the application provided was a "formula for computing an updated alarm limit." *Id.*, at footnote 14. The claims in *Diehr*, however, are not limited to the isolated step of "programming a digital computer," the Court found; rather, they describe a process of curing rubber beginning with the loading of the mold and ending with the opening of the press and the production of a synthetic rubber product that has been perfectly cured – a result heretofore unknown in the art. *Id.*, at footnote 15. As the *Diehr* Court explained, "[w]hen a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, is performing a function which the patent laws were designed to protect (e.g.,

transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of 35 U.S.C. §101." *Id.*, at 192. Because the Court did not view respondents' claims as an attempt to patent a mathematical formula, but rather to be drawn to an industrial process for the molding of rubber products, the *Diehr* Court affirmed the judgment of the Court of Customs and Patent Appeals. *Id.*, at 192, 193.

Finally, in finding the commodity claims in *Bilski* to be non-statutory subject matter, the *Bilski* Court explained that:

> "Petitioners' remaining claims are broad examples of how hedging can be used in commodities and energy markets. *Flook* established that limiting an abstract idea to one field of use or adding token post solution components did not make the concept patentable. That is exactly what the remaining claims in petitioners' application do."

Bilski, *supra*, at 3231.

Simply put, insignificant extra-solution activity will not transform an unpatentable principle into a patentable process. *Diehr*, *supra*, at 191, 192. To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection. *Id.*, at 192.

It could be argued that calling an element an "insignificant extra-solution activity" is tantamount to disregarding that element in the 35 U.S.C. §101

analysis in violation of this Court's precedent that a "claims . . . as a whole" analysis must be performed when making any 35 U.S.C. §101 determination. *Id.*, at 188. That argument misses the mark of this Court's precedent on "insignificant extra-solution activity." While it is true that a claim must be viewed as a whole, not every element of a claim must be given the same weight. Indeed, it is only by looking at the claim as a whole that the elements of the claim that are central can be separated from those that are merely extra-solution activity.

As this Court has explained, a determination of which elements of a claim amount to nothing more than insignificant extra-solution activity plays an important role in deciding whether a claim is subject matter patentable under 35 U.S.C. §101. However, recognizing when an element amounts to an insignificant extra-solution activity is not always easy. This Court has provided valuable guidance on this point in *Bilski* and in the *Diehr*, *Flook*, and *Benson* decisions. *Bilski*, *supra*, at 3231. The Federal Circuit has recently provided further useful guidance on this issue in *Classen Immunotherapies, Inc. v. Biogen IDEC*, 2011 U.S. App. LEXIS 18126, * (Fed. Cir. 2011).

In *Classen*, the Federal Circuit was asked to decide whether three patents on a method for improving an immunization schedule involving method claims directed to identifying a safe vaccine regimen and involving a step of immunizing mammals is patentable subject matter. The patents before the Court were U.S. Pat. Nos. 6,638,739; 6,420,139; and 5,723,283.

Following the precedent of this Court on token extra-solution activity, in *Classen*, the court impliedly cast aside the notion that generally all transformative steps are patentable subject matter and introduced a "subject matter patentability filter" through which all transformation steps in a claim must pass. *Id.*, at *24-25. This "subject matter patentability filter" may be helpful in weeding out transformative steps in a process that add no meaningful limitations to the claim and hence amount to token extra-solution activity. In *Classen*, claims of one of the three patents before the court, the '283 patent, failed to pass the "subject matter patentability filter," impliedly because they amounted to an insignificant or token activity. *Id.*, at *25-26. As the court explained, "[t]he 'immunizing' in the '283 patent refers [only] to the gathering of published data, while the 'immunizing' of the '139 and '739 patent claims is the physical implementation of the mental step claimed in the '283 patent." *Id.*, at *26. The different treatment given by the court to the two sets of patents turned on the different construction the court gave to the two sets of claims.

In both patents, the court keyed in on the "immunizing" step. In the '139 and '739 patents, the recitation occurred *after* a screening step was performed to derive a subject specific immunization schedule for use in the immunizing step and in the '283 patent, the immunizing step was recited *before* a comparing step to generate data merely for comparison to known information in that comparing step. *Id.*, at *27. While facially both sets of patents recited

"immunizing" steps that were transformative, the court opined that the "immunizing" step of the '283 patent failed to pass through the "subject matter patentability filter." *Id.*, at *25-26. The court held that a transformation for data gathering purposes to develop a body of knowledge, as was recited in the '283 patent, is not patentable, while a transformation that "puts this knowledge to practical use," as was recited in the '139 and '739 patents comports with 35 U.S.C. §101. *Id.*, at *26-27. Thus, according to *Classen*, gathering data simply for the purpose of developing a body of knowledge is extra-solution activity whereas gathering data for practical application in later steps in the method is not extra-solution activity.

Thus, in both representative claims 1 and 46 of *Prometheus*, the "determining" step is not merely token extra-solution data gathering activity, which was the death knell of the '283 patent in *Classen*, since the knowledge that is collected in this step is put to practical use in the other steps in the claim. The "determining" step generates data *applied to enable adjustment of the drug dosage in the recited observed correlation*. It manipulates the chemistry of a body to this application, or, as the *Classen* court put it, "puts this knowledge to practical use." *Ibid.* Additionally, claim 1 further recites an "administering" step which further generates data *applied to enabling the adjustment of the drug dosage in the recited observed correlation*. As such, the transformative steps of "administering" and "determining" are "essential" and central to the claim and so should be included in the

35 U.S.C. §101 determination, not treated as token extra-solution activity and disregarded in the 35 U.S.C. §101 analysis.

III. The clue to patentability should lie in whether steps that are central to the claim (i.e., not token extra-solution activity) have a "physical" or "virtual" link to a specific physical or tangible object. The *Prometheus* claims have both a "physical" and a "virtual" link and so should be subject matter patentable under 35 U.S.C. §101.

Benson, *Flook*, *Diehr*, and *Bilski* stand for the proposition that a process claim taken as a whole and excluding extra-solution activity must be tailored narrowly enough to encompass only a particular application of a fundamental principle (i.e., a law of nature, natural phenomenon, or an abstract idea) rather than to preempt the principle itself. The 35 U.S.C. §101 challenge post-*Bilski* thus is to define the boundary line of an invention involving an abstract idea, law of nature, or natural phenomenon beyond which the invention preempts one of these categories and is therefore unpatentable subject matter, and within which it is patentable.

While it is expected that there is no bright line rule that will work in every case, for guidance on where to define this boundary line, the *Bilski* Court pointed to the trilogy of *Benson-Flook-Diehr* as precedent. *Bilski*, *supra*, at 3231. From the *Benson-Flook-Diehr*

spectrum of inventions involving a fundamental principle, the threshold for subject matter patentability may be gleaned; to wit, the existence of a link of the invention to a specific physical or tangible object. The invention in *Diehr* was held patentable because it connected to (more specifically, the electrical signals or data generated by the software *manipulated*) the physical and, in this case, also tangible objects of a "mold" and a "press" through the steps of "loading of the mold" and "opening of the press." Patentability in *Flook* failed since the claims were without any such link.

More specifically, the *Diehr* Court stated that "[w]e were careful to note in *Flook* that the patent application did not purport to explain how the variables used in the formula were to be selected, nor did the application contain any disclosure relating to chemical processes at work or the means of setting off an alarm or adjusting the alarm limit." *Diehr*, *supra*, at footnote 14. All the application provided was a "formula for computing an updated alarm limit." *Ibid.* One interpretation of these comments on *Flook* in *Diehr* is that there was no "link" of the data to a physical or tangible object. "Diehr's claims, however, are not limited to the isolated step of programming a digital computer," the Court explained. *Id.*, at footnote 15. Rather, "they describe a process of curing rubber beginning with the loading of the mold and ending with the opening of the press and the production of a synthetic rubber product that has been perfectly cured – a result heretofore unknown in the art." *Ibid.* In other words, there was a "link"

of the data to a specific physical or tangible object (i.e., a "manipulation" by the data of a physical or tangible object).

Hence, in *Diehr*, software that *manipulates* a specific physical or tangible object (i.e., "physically links" to a physical or tangible object) is patentable subject matter (e.g., the software manipulated data in *Diehr* signaled a device when to open the molding press and remove the cured rubber product). The same should be considered true for "virtual links," where the data that are manipulated, while not physical or tangible objects themselves, *are representations of a specific physical or tangible object*, as in the fifth claim of *Morse* (e.g., Morse code dot and dash signs representing the change in state of a physical (e.g., switch) or tangible object, such as on-off tones, lights, or clicks, in telegraphic use were held patentable). *O'Reilly v. Morse*, 56 U.S. 62, 112 (1853).[5] An invention that manipulates data representing a specific physical or tangible object (i.e., that contains a "virtual link") should also be subject matter patentable under the Supreme Court's *Morse* precedent.

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[5] Morse's fifth claim recites: "Fifth. I claim as my invention the system of signs, consisting of dots and spaces, and of dots, spaces, and horizontal lines, for numerals, letters, words, or sentences, substantially as herein set forth and illustrated, for telegraphic purposes." *Morse*, *supra*, at 86. The Court "perceive[d] no well founded objection to the description which is given of the whole invention and its separate parts, nor to his right to a patent for the first seven inventions set forth in the specification of his claims. The difficulty arises on the eighth." *Id.*, at 112. See also *id.*, at 94-95 for characters recorded and how they are read.

Also instructive on "virtual links," that is, the idea that *manipulation of data representing a physical or tangible object* is sufficient to provide patentable subject matter, is *In re Abele*, 684 F.2d 902 (CCPA 1982). In *Abele* the Court of Customs and Patent Appeals held unpatentable a broad independent claim reciting a process of graphically displaying variances of data from average values. *Id.*, at 908. That claim did not specify any particular type or nature of data; nor did it specify how or from where the data was obtained or what the data represented. One dependent claim, however, was drawn to patent-eligible subject matter where it recited that "said data is X-ray attenuation data produced in a two dimensional field by a computed tomography scanner." *Id.*, at 908-909. As was explained by the Federal Circuit in *In re Bilski*, 2008 U.S. App. LEXIS 22479, *, 545 F.3d 943, 88 U.S.P.Q.2D (BNA) (Fed. Cir. 2008) (en banc), the data in *Abele*: "clearly represented physical and tangible objects, namely the structure of bones, organs, and other body tissues. Thus, the transformation of that raw data into a particular visual depiction of a physical object on a display was sufficient to render that more narrowly claimed process patent-eligible." *Id.*, at *50.

This link of data to something "real" (either by "physical" manipulation of a physical or tangible object, or by "virtual" manipulation of data representing a physical or tangible object) may thus provide a useful clue to the patent eligibility of inventions involving processes, under this Court's *Diehr* and *Morse* precedent. The term "physical" or "tangible" covers all things that exist in the real world rather than things

that are imaginary or that exist only in the mind. Anything existing in the real world includes both those things that can be directly perceived, touched, or manipulated, and physical phenomena, such as electrical signals, electromagnetic radiation, or chemical properties which, while existing in the real world, may only be perceived or manipulated indirectly, such as with the assistance of a machine or apparatus, or by a chemical reaction. The "physical link" and "virtual link" patent claim approach may thus be helpful in defining that boundary line beyond which a claim preempts a fundamental principle (i.e., a law of nature, natural phenomenon, or an abstract idea) and within which the claim does not.

In the context of this threshold, the patentability of the claims in *Prometheus* becomes clearer. From the discussion in Part II above, the "administering" step and the "determining" step are not token extra-solution activity and so should be included in the 35 U.S.C. §101 determination. From the following discussion, the "determining" and "administering" steps each provide a "physical" link to (i.e., they each "manipulate") a specific physical or tangible object (i.e., blood). Thus, when considered as a whole, the claim that includes these steps as something more than token extra-solution activity is patentable subject matter, since the claim is drawn to manipulating a specific physical or tangible object, and is not just a natural phenomenon, abstract idea, or law of nature, or a process that completely preempts one of these. See *Diehr*, *supra*, at 192-193.

The "determining" and "administering" steps in *Prometheus* plainly manipulate a specific physical or tangible object. The "administering" step is a transformation of the human body and of its components following the administration of a particular class of drugs and the various chemical and physical changes of the drugs into their metabolites, *Prometheus*, at *24. This transformative step is not merely gathering data. Rather, as explained in Part II above, the "administering" step generates data applied to enable adjustment of the drug dosage in the recited observed correlation. The "determining" step necessarily also involves a manipulation, such as the high pressure liquid chromatography method specified in several of the asserted dependent claims, or some other modification of the substances to be measured, which is necessary to extract the metabolites from a bodily sample and determine their concentration. *Id.*, at *26. This transformative step likewise is not merely data gathering. Rather, it too generates data applied to enabling the adjustment of the drug dosage in the recited observed correlation. The claims in *Prometheus* hence "physically link" to (i.e., they "directly manipulate") a physical or tangible object (e.g., the administered drug "physically" so manipulates the blood chemistry in the "administering" step and the body chemistries are so manipulated to extract the 6-thioguanine level by the "determining" step). Just as the software manipulated data in *Diehr*, signaling a device when to open the molding press and remove the cured rubber product, rendered the claim as a whole to be subject matter patentable, so too the *Prometheus* "administering" and "determining" steps

should be found to make the claim as a whole subject matter patentable.

In addition, the "observed correlation" step, in combination with the "determining" step, and, in the case of claim 1, also the "administering" step, provide a "virtual link" to (i.e., the observed correlation data manipulates *representations of*) a specific physical or tangible object (i.e., the blood) which alternatively and additionally makes the claims subject matter patentable. Apposite is *Morse*, *supra*, at 112. See also *Abele*, *supra*, at 908-909.

The "observed correlation" recited in the *Prometheus* claims manipulates data representing a specific physical or tangible object. The "level of 6-thioguanine" is data representing a specific physical or tangible object (i.e., the blood, and in particular, the 6-thioguanine in the blood). Those data, representing a specific physical or tangible object, are manipulated by the association of those data with a drug adjustment indicator generated by the "observed correlation" step. The "association" is by the tagging of the 6-thioguanine level data *with a specific drug adjustment level indicator* (i.e., the "need to increase" or the "need to decrease" data which is generated by the "observed correlation" step). The indicator biases and hence "manipulates" the "level of 6-thioguanine" data toward increased drug administration if the level of 6-thioguanine is less than about 230 pmol per $8x10^8$ red blood cells and toward decreased drug administration if the level is greater than 400 pmol per $8x10^8$. It is the biasing or manipulation of the "level of 6-thioguanine" data in the direction of the drug

adjustment indicator generated by the "observed correlation" step that provides the manipulation of the level of 6-thioguanine data, which represents the physical or tangible object (i.e., the blood). In effect, the drug adjustment level indicator generated through the step of the "observed correlation" defines a direction for the "level of 6-thioguanine" data that directs further drug administration.

Without the "determining" step and in the case of claim 1, also the "administering" step, the "observed correlation" does not provide a "virtual" link to data representing a physical or tangible object and so amounts to nothing more than textbook knowledge, the claiming of which would preempt a natural phenomenon, abstract idea, or law of nature in violation of 35 U.S.C. §101 under this Court's precedent. However, this is not the case in *Prometheus*. As indicated in Parts I and II above, the claim must be considered as a whole, and neither the "administering" or "determining" step is token extra-solution activity. And as explained in Part III above, the "observed correlation" in the presence of "administering" and/or "determining" steps has the necessary *virtual link* to (i.e., the "observed correlation" data manipulates *representations of*) a specific physical or tangible object that further makes the claims subject matter patentable under this Court's precedent.

It is the enabled adjustment of the drug dosage in the recited "observed correlation" of the specific sample of data generated by the "administering" and "determining" steps in claim 1 and the "determining" step in claim 46 that gives rise to the "virtual link."

Without the chemical transformative steps of "administering" and "determining" that work up the body chemistry into a specific sample of data that enables the adjustment of the drug dosage in the recited "observed correlation" recited in the *Prometheus* claims; that is to say, if an "observed correlation" is removed from a specific sample of data and is done in a vacuum, it is no different than an "observed correlation" taught in medical books (i.e., general medical information) which is "part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none." *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

The "observed correlation" recited in the *Prometheus* claims manipulates data representing a physical or tangible object because the enabled adjustment of the drug dosage in the recited "observed correlation" is possible by use of the specific sample of data that is generated by the "determining step" (i.e., the manipulation occurs through the "observed correlation" in combination with the "determining" step), and, in the case of claim 1, the enabled adjustment of the drug dosage in the recited "observed correlation" is also possible by use of the specific sample of data that is generated by the "administering" step (i.e., the manipulation occurs in this case through the "observed combination" in combination with "administering" and "determining" steps). This manipulation provides each of claims 1 and 46 with a "virtual link" to a physical or tangible object, thereby providing a further basis for the subject matter patentability of the *Prometheus* claims under 35 U.S.C. §101, in view

of *Morse*, *supra*, at 112. See also *Abele*, *supra*, at 908, 909. This "virtual link" basis for subject matter patentability of the *Prometheus* claims is independent from and additional to the subject matter patentability that the transformative "administering" and "determining" steps provide to these claims through the creation of "physical links" to a specific physical or tangible object (i.e., the blood), under *Diehr*, *supra*, at footnote 15.

Just as the software manipulated data in *Diehr* signaling a device when to open the molding press and remove the cured rubber product was found by this Court to be subject matter patentable, so too the *Prometheus* "administering" and "determining" steps that provide "physical" links to the blood chemistry of a body should be subject matter patentable under 35 U.S.C. §101. Alternatively, or in addition, just as the manipulated data representations of a physical or tangible object in the fifth claim of *Morse* (e.g., Morse code dot and dash signs representing the change in state of a physical (e.g., switch) or tangible object, such as on-off tones, lights, or clicks, in a telegraphic use) was found by the *Morse* Court to be subject matter patentable, so too the *Prometheus* enabled adjustment of the drug dosage in the recited "observed correlation" step in combination with the "determining" step, and, in the case of claim 1, also the "administering" step, provide a "virtual link" to (i.e., they manipulate representations of) a specific physical or tangible object (i.e., blood) and so should likewise be subject matter patentable under 35 U.S.C. §101.

CONCLUSION

The judgment of the court of appeals reversing the district court's ruling under 35 U.S.C. §101 should be affirmed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF MICROSOFT CORPORATION, EMC CORPORATION, AND INTEL CORPORATION AS *AMICI CURIAE* IN SUPPORT OF NEITHER PARTY

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BRIEF OF MICROSOFT CORPORATION, EMC CORPORATION, AND INTEL CORPORATION *AS AMICI CURIAE* IN SUPPORT OF NEITHER PARTY

INTEREST OF *AMICI CURIAE*[1]

This case presents the question whether the diagnostic method claimed by respondent is eligible for patenting. More broadly, this case brings to the Court for the second time in three years—and the third time in six years—the question of when a process is eligible for patenting under Section 101 of the Patent Act.

Amici curiae have a substantial interest in the correct resolution of that issue. *Amici* are among the leading companies in their respective fields. *Amici* own, collectively, tens of thousands of patents, which they rely upon to protect their substantial investments in research and development. They are among the most innovative companies in America. But they also frequently are accused of infringing all manner of patents. *Amici* thus can offer a uniquely balanced viewpoint on questions surrounding patent eligibility under Section 101.

Amici curiae believe that rigid and technology-specific standards for patent eligibility, such as the

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[1] Pursuant to this Court's Rule 37.3(a), letters of consent from all parties to the filing of this brief have been submitted to the Clerk. Pursuant to this Court's Rule 37.6, *amici* state that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than *amici* or their counsel made a monetary contribution intended to fund the preparation or submission of this brief.

"machine-or-transformation test" adopted by the Federal Circuit in *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008) (en banc) and addressed by this Court in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), hamper innovation by sharply limiting the availability of patents for emerging technologies. Yet *amici* also believe that the malleability and indeterminacy of post-*Bilski* administrative policy and judicial case law hamper innovation for new and old technologies alike. *Amici* experience first-hand—both in the patent application process and in patent litigation—the difficulty of assessing patent eligibility under Section 101 and suffer the costs of that uncertainty.

Amici urge this Court to confirm the broad sweep of inventions eligible for patenting by returning to its early case law and reaffirm the basic standard for patent eligibility that focuses on the use of certain means to create a useful practical result in the physical world. That historical standard is neither technology-specific, nor indeterminate; it respects Congress's broad statutory language in Section 101; it is consistent with the "abstractness" standard articulated in *Bilski*; it does not usurp the role Congress assigned to Sections 102, 103, and 112 of the Patent Act; and it is sufficient to prevent an inventor from claiming a law of nature, natural phenomena, or abstract idea by limiting claims to what the inventor has actually invented and rendered of use to the world.[2]

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[2] *Amici* take no position on the patentability of the particular claims at issue here. *Amici*'s expertise includes the invention of new computer-implemented processes, which are patent eligible when properly claimed. *See* 35 U.S.C. § 100(b) ("The term process . . . includes a new use of a known . . . machine.").

SUMMARY OF ARGUMENT

Section 101 of the Patent Act polices patent eligibility and nothing more. The statute is crafted broadly to allow the inventor of any "new and useful process, machine, manufacture, or composition of matter" to seek a patent therefor and ultimately to "obtain a patent therefor" if the invention satisfies "the conditions and requirements" of the entire Patent Act. Unfortunately, as the case law and administrative practice have developed, Section 101 has been set to other tasks—tasks Congress assigned to other sections of the Patent Act. As a result, the property rights inherent in many patents—particularly patents that claim processes—have been unsettled—a state of affairs *amici* believe this Court can readily correct by reference to the text of the Patent Act and this Court's early patent-eligibility decisions.

I. Congress set forth the patent eligibility of inventions in broad terms. Combining the statutory definition of process under Section 100(b) with Section 101 shows that "any process, art, or method" including the "new use of a known process" is patent eligible. The scope of this congressional decree ensures that patents are broadly available for diverse inventions in all fields of technology—even those fields as yet unknown.

The Court has recognized only appropriate limits on that scope. While one may patent a process, a principle—*i.e.*, a law of nature, natural phenomena, or abstract idea—remains free for all to use. But recent efforts by lower courts and the PTO to locate the boundary separating patent-eligible processes from abstract ideas have been unsuccessful.

II. In analyzing the eligibility of an invention for a patent, courts and the PTO today feel empowered to parse the claimed invention into the "underlying invention" and those aspects that are "conventional" or "obvious" or insignificant "extra- or post-solution activity." The recited elements identified as "conventional" or "extra-solution activity" are then disregarded, and the "underlying invention" alone is analyzed to determine whether it is a statutory process or merely an abstract idea. This approach has no statutory basis and—due to its subjective nature—neither the lower courts nor the PTO has been able to articulate a principle that allows one to determine consistently what portions of a particular claim may be disregarded under Section 101.

Too often, courts and the PTO make a subjective judgment, labeling portions of a claim "extra-solution" or "conventional" on the basis of individual judgments regarding that portions relative significance to the "underlying invention." The subjective nature of these judgments allows the decision maker to consider what parts of a claim may support the claim's *patentability* under the Patent Act. But *amici* believe that such analysis is inappropriate for the threshold inquiry—whether the subject matter of the claim as a whole is *eligible* for patenting under Section 101.

III. *Amici* urge a return to the historical standards of patent eligibility developed in this Court's decisions in *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1853), *The Telephone Cases*, 126 U.S. 1 (1888), and *Tilghman v. Proctor*, 102 U.S. 707 (1881). These decisions—which themselves established the non-statutory exceptions to patent eligibility invoked by petitioners here—instruct courts to look to the claim

as a whole and determine whether the invention claims the use of *certain means* to produce a *certain useful result*. Under this standard, to be eligible for patenting, a claimed process invention includes both the means and the result, *i.e.*, one or more disclosed physical things used to produce a practical result or effect in the physical world. But that is all that is required to establish its patent eligibility. A return to this standard would, *amici* believe, result in better, more objective decisions by the lower courts and the PTO with respect to patent *eligibility* and assign other assertions of patent *invalidity* (such as the lack of novelty of which petitioners complain) for analysis under the provisions designated by Congress in the Patent Act: 35 U.S.C. §§ 102, 103, and 112. And it would ensure that the technologies of tomorrow, no less than the technologies of today, will have access to our patent system and the investments in innovation that system so effectively promotes.

ARGUMENT

I. SECTION 101 REFLECTS A CONGRESSIONAL JUDGMENT THAT INNOVATION SHOULD BE ENCOURAGED ACROSS TECHNOLOGIES KNOWN AND UNKNOWN.

> [T]he very first official thing I did, in my administration—and it was on the very first day of it, too—was to start a patent office; for I knew that a country without a patent office and good patent laws was just a crab, and couldn't travel any way but sideways or backwards.

Mark Twain, *A Connecticut Yankee in King Arthur's Court* 64 (Harper & Brothers 1889).

Anticipating Twain by a century, the Founders established the constitutional and statutory bases for patentability and patent eligibility when the Nation was still in its infancy. *See Graham v. John Deere Co.*, 383 U.S. 1, 5-11 (1966).

Article I of the Constitution empowers Congress "[t]o promote the Progress of Science and useful Arts, by securing . . . to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. Const. art. I, § 8, cl. 8. The first Congress exercised this authority by enacting the Patent Act of 1790. That Act provided "[t]hat upon the petition of any person or persons . . . setting forth, that he, she, or they, hath or have invented or discovered any useful art, manufacture, engine, machine or device, or any improvement therein," a patent could be granted to "such petitioner or petitioners." Act of Apr. 10, 1790, ch. 7, § 1, 1 Stat. 109, 109-10.

The law today remains substantially the same: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor." 35 U.S.C. § 101.

This language is broad and encompassing; this Court has said it embraces "'anything under the sun that is made by man.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting S. Rep. No. 82-1979, at 5 (1952)). Incorporating the definition of "process" provided in 35 U.S.C. § 100(b), it states that "*any* process, art, or method" is eligible for a patent so long as it is "new and useful." *Id.* §§ 100(b), 101 (emphasis added). This Court has long recognized that, by using such expansive language in Section 101, including "the comprehensive 'any,' Congress plainly contemplated that the patent laws would be

given wide scope." *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 308). That "wide scope" ensures that patents are broadly available for diverse inventions in all fields of technology—even those fields as yet unknown that will drive progress for future generations. *See ibid.* ("Congress took this permissive approach to patent eligibility to ensure that 'ingenuity should receive a liberal encouragement.'") (quoting *Chakrabarty*, 447 U.S. at 308-09, in turn quoting 5 Writings of Thomas Jefferson 75-76 (Washington ed. 1871)).

But this Court has long and no less certainly held that the language of Section 101 is not so broad as to allow one to patent "laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). Recent judicial efforts to locate the boundary separating patent-eligible processes from abstract ideas have been unsatisfying as reflected in the fact that this Court has once again taken up the question. Indeed, commentators have observed that it has proven to be "one of the most confounding and potentially critical areas of patent law." Peter S. Menell, *Forty Years of Wondering in the Wilderness and No Closer to the Promised Land: Bilski's Superficial Textualism and the Missed Opportunity to Return Patent Law to Its Technology Mooring*, 63 Stan. L. Rev. 1289, 1290 (2011).

II. THE EXTRA-SOLUTION ACTIVITY ANALYSIS NOW EMPLOYED BY COURTS AND THE PTO IS SUBJECTIVE AND THEREFORE INDETERMINATE.

A. Last year, this Court reviewed *In re Bilski*, the Federal Circuit's attempt to create a universal standard for reviewing the eligibility of process and method claims under Section 101. 545 F.3d 943, 956-

58 (Fed. Cir. 2008) (en banc). While this Court affirmed the Federal Circuit's holding that Bilski's claimed invention was too abstract to be eligible for patenting, this Court also made clear that the Federal Circuit incorrectly treated the machine-or-transformation test as the sole test for statutory eligibility. *Bilski v. Kappos*, 130 S. Ct. at 3226. Instead, the "test" was, at most, "just an important and useful clue" as to whether the claimed invention was within the scope of statutory subject matter defined by Section 101. *Ibid.*

But, in truth, no lower court had treated the machine-or-transformation test as the *sole* determinant of patent eligibility. The courts and the PTO, following language in earlier court decisions, have recognized a "corollary to the machine-or-transformation test" that excludes from the eligibility analysis any claim element that the decision maker considers to be "extra-solution activity." *In re Bilski*, 545 F.3d at 957 & n.14; *see also* Interim Guidance for Determining Subject Matter Eligibility for Process Claims in View of *Bilski v. Kappos*, 75 Fed. Reg. 43922, 43925 (July 27, 2010). Under that standard, "even if a claim recites a specific machine or a particular transformation of a specific article, the recited machine or transformation must not constitute mere 'insignificant postsolution activity'" lest the claim be rendered ineligible. *In re Bilski*, 545 F.3d at 957. And this "corollary" has been broadly applied by the lower courts and the PTO and not limited merely to *post*-solution activity; it applies with equal force to "a pre-solution step," a "step in the middle of the claimed process," and "postsolution activity"—any claim elements the courts or the PTO determined to be "insignificant." *Id.* at 957 & n.14 (internal quotation marks omitted).

The Federal Circuit has found that this extra-solution-activity corollary encompasses claim elements that amount, in its judgment, only to "mere" data gathering. *See In re Bilski*, 545 F.3d at 963 ("This court and our predecessor court have frequently stated that adding a data-gathering step to an algorithm is insufficient to convert that algorithm into a patent-eligible process."). And, indeed, the district court below, prior to either *Bilski* decision, found the claims here ineligible under this carve-out for "merely data-gathering." *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, No. 04cv1200, 2008 WL 878910, at *6 (S.D. Cal. Mar. 28, 2008).

But the Federal Circuit, reviewing this case after a remand from this Court in light of *Bilski v. Kappos*, disagreed. It found that the steps that the district court identified as mere data gathering instead implicated transformations of matter that were "central to the claims rather than merely insignificant extra-solution activity." Pet. App. 19a. Prometheus's claim therefore satisfied the machine-or-transformation test, which, the court of appeals concluded, "le[d] to a clear and compelling conclusion" that Prometheus's process was eligible for patenting. *Id.* at 14a.

The Federal Circuit's most recent Section 101 decisions similarly turn on an analysis of the significance of physical elements to the claimed invention. Its recent decision in *CyberSource Corp. v. Retail Decisions, Inc.*, No. 2009-1358 (Fed. Cir. Aug. 16, 2011), put it in very stark terms: "Regardless of what statutory category ('process, machine, manufacture, or composition of matter,' 35 U.S.C. § 101) a claim's language is crafted to literally invoke, we look to the

underlying invention for patent-eligibility purposes." *CyberSource*, slip op. at 17 (emphasis added).

The claim in *CyberSource* recited "a computer readable medium," which the court recognized meant "a disk, hard drive, or other data storage device." *CyberSource*, slip op. at 14. But the court held that these objects were not sufficiently integral to the "underlying invention" to confer eligibility; the "underlying invention," the Federal Circuit held, included only the "algorithm" stored on the device. *Id.* at 17-18. That algorithm, standing alone, the court ruled, was not a "machine," "manufacture," or "process" eligible for patenting. *Id.* at 16-17. So while blank disks, empty hard drives, and other storage devices all indisputably are machines or manufactures *eligible* for patent protection—claims to such inventions, of course, might be invalid for other reasons such as lack of novelty or obviousness—the court concluded that the addition of software instructions to the physical media may fundamentally compromise that eligibility.[3]

CyberSource also relied on the doctrine that a claim including elements "drawn to a mental pro-

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[3] Notably, the Federal Circuit sometimes has taken the precisely opposite approach after *Bilski v. Kappos*, reading physical elements *into* a method claim in order to hold it eligible for patenting. For example, in *Research Corp. Techs, Inc. v. Microsoft Corp.*, 627 F.3d 859 (Fed. Cir. 2010), the Federal Circuit ruled that claim 1 to a "method for the halftoning of gray scale images" that recited using a "comparison" of the image to a "mask . . . comprised of a random non-deterministic, non-white noise single valued function" was patent eligible because it concluded that the claimed method incorporated physical elements such as a "printer" and "a memory" that were recited in other claims. *Id.* at 865, 869.

cess" is ineligible. *CyberSource*, slip op. at 16. As do petitioners. Pet. Br. 19, 27. *Amici* do not disagree, that if *every* step of a process claim can be performed in the human mind, that process is unpatentable. But the *CyberSource* court extended that principle to apply to machines or manufactures that replicate mental steps—an untenable extension. *See generally Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939) (finding claims that incorporated a mathematical formula readily calculable by the mind as patent eligible). For example, a new computer-implemented process may cause a machine to replicate steps, which could be performed—typically more slowly—in the human mind. But the use of that machine is statutorily eligible. *See* 35 U.S.C. § 100(b) ("The term 'process' . . . includes a new use of a known . . . machine."). And petitioners seek an expansive application of the mental steps doctrine, such that claims that "culminate" with a "mental step" are ineligible. Pet. Br. 19.

B. This mode of analysis requiring judges and patent examiners to parse the significance of claim elements in order to locate the "underlying invention" encourages them to disregard tangible elements explicitly recited in the claims in order to find the claims "abstract" and has little to commend it. It has no connection to the text of Section 101; is irreconcilable with this Court's admonition that "there is no legally recognizable or protected 'essential' element, 'gist' or 'heart' of the invention in a combination patent," *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 345 (1961); and is utterly indeterminate, as the litigation of this case amply demonstrates. Whether an invention is eligible for a patent should not be made to depend upon the views of a judge, who likely has little expertise in the field of

use, as to whether recited physical elements are central or insignificant.

Yet, petitioners here argue that this indeterminacy on a question as basic as whether an invention is *eligible* for a patent is compelled by this Court's precedents—particularly *Parker v. Flook*, 437 U.S. 584 (1978). Pet. Br. 30-31. That contention places more weight on *Flook* than it can bear.

In *Flook*, the claim recited a "method for updating the value of at least one alarm limit on at least one process variable" involved in the "catalytic chemical conversion of hydrocarbons." 437 U.S. at 596. One step of the claimed method included calculating a "new alarm base" using a mathematical formula. *Id.* at 597. The Court first assumed "that the formula is the only novel feature" of the claimed method. *Id.* at 588. Then, the Court asked whether the discovery of the formula "makes an otherwise conventional method [patent] eligible." *Ibid.* The patent applicant, Flook, argued that the other steps of the claim, particularly the "post-solution" activity of adjusting the alarm limit, made the process eligible.

This Court disagreed: "The notion that post-solution activity, *no matter how conventional or obvious in itself*, can transform an unpatentable principle into a patentable process exalts form over substance." *Flook*, 437 U.S. at 590 (emphasis added). The Court thus held that the claimed method was ineligible under Section 101 because once the claimed "algorithm is assumed to be *within the prior art*, the application, considered as a whole, contains no patentable invention." *Id.* at 594 (emphasis added).

Justice Stewart criticized the *Flook* majority's analysis as confusing patent *eligibility* under Section

101 with patentable *novelty* under Section 102 and patentable *nonobviousness* under Section 103. *See Flook*, 437 U.S. at 600 (Stewart, J., dissenting) ("The Court today . . . strikes . . . [a] damaging blow at basic principles of patent law by importing into its inquiry under 35 U.S.C. § 101 the criteria of novelty and inventiveness."). That criticism still has currency today. *See, e.g.*, 1 Donald S. Chisum, *Chisum on Patents* § 1.03[6][e] (2010) ("[D]espite the Court's protestations to the contrary, its analysis of statutory subject matter under Section 101 does in a sense import concepts of novelty and nonobviousness.").[4]

C. In light of these issues, it is perhaps not surprising that this Court moved to clarify *Flook* shortly thereafter in *Diamond v. Diehr*. In *Diehr*, this Court rejected the government's argument that *Flook* required a court to parse the claims to determine the novelty of each element *vel non*. 450 U.S. at 189 n.12. Relying on *Cochrane v. Deener*, 94 U.S. 780 (1877) and *Gottschalk v. Benson*, 409 U.S. 63 (1972), the Court held that, in analyzing patent eli-

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[4] Petitioners' argument similarly seems to speak more in terms of novelty and obviousness than patent eligibility. Petitioners complain that the inventors "freely disclosed" their invention before filing the patents at issue, Pet. Br. 5; and that certain claim steps are "well known and have been used by physicians and researchers for decades," *id.* at 24, or "obvious," *id.* at 30 (internal quotation marks omitted). Even if true, these allegations ought to have no bearing upon the question of eligibility for patenting of respondent's claimed process. Instead, they would bear only upon other defenses of patent invalidity that would remain open to the lower courts on remand should the Court hold one or more of respondent's claims patent eligible.

gibility, it is "inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements." *Id.* at 188.

Section 101, the Court observed, was not the only safeguard against inappropriately issued patents. *Diehr*, 450 U.S. at 191. Even if a claimed invention were patent eligible, "it may later be determined that the [claimed invention] is not deserving of patent protection because it fails to satisfy" Sections 102 (novelty) and 103 (nonobviousness). *Ibid.* In addition, an invention cannot be patented if the inventor's patent fails to satisfy the many requirements of Section 112, including providing "a written description of the invention," "enabl[ing]" those of skill in the art to make and use the invention, and "particularly pointing out and distinctly claiming" the invention. 35 U.S.C. § 112. Accordingly, novelty "is of no relevance in determining whether the subject matter of the claim falls within the § 101 categories of possibly patentable subject matter." *Diehr*, 450 U.S. at 188-89. Indeed, "[t]he fact that one or more of the steps in respondents' process may not, in isolation, be novel or independently eligible for patent protection is irrelevant to the question of whether the claims as a whole recite subject matter *eligible* for patent protection under § 101." *Id.* at 193 n.15.

To reconcile this reasoning with that of *Flook*, *Diehr* cast *Flook* as a decision that involved only "token" post-solution activity. *Diehr*, 450 U.S. at 192 n.14 ("[A] mathematical formula does not become patentable subject matter merely by including in the claim for the formula token postsolution activity . . . ."). Such "insignificant postsolution activity,"

Diehr observed, "will not transform an unpatentable principle into a patentable process." *Id.* at 191-92.[5]

D. From *Diehr*'s reservation regarding the patent eligibility of a claim for which the only connection to the physical world was "token" or "insignificant post-solution activity," the lower courts and the PTO now draw license to dissect claimed inventions into those portions that are "insignificant" or "extra-solution" and those that truly represent "the underlying invention." Petitioners rely on the very same reservation, Pet. Br. 30-31, to argue that certain steps in the claims at issue are "data-gathering" steps using "ordinary means" that cannot weigh towards patentability, *id.* at 35.

Yet, this is precisely the type of "dissect[ion]" that *Diehr* found "inappropriate" for an analysis of "whether the claims *as a whole* recite subject matter *eligible* for patent protection." *Diehr*, 450 U.S. at 188, 193 n.15 (first emphasis added). And predictably the "insignificance," or not, of claim elements has proven to be only in the eye of the beholder, as pa-

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[5] Many commentators did not think *Flook* and *Diehr* could be reconciled so easily. *See, e.g.*, James J. Myrick & James A. Sprowl, *Patent Law for Programmed Computers and Programmed Life Forms*, 68 A.B.A. J. 920, 923 (1982) ("*Flook* cannot be reconciled with *Diehr* and *Chakrabarty* on any but superficial grounds. Under *Flook* machines and methods realized by feeding new instructions into universal machines simply cannot be patented."); Susan J. Marsnik & Robert E. Thomas, *Drawing a Line in the Patent Subject-Matter Sands: Does Europe Provide a Solution to the Software and Business Method Patent Problem?*, 34 B.C. Int'l & Comp. L. Rev. 227, 252 (2011), *available at* http://lawdigitalcommons.bc.edu/iclr/vol34/iss2/1 ("It is hard to reconcile the different results in *Flook* and *Diehr* given the strong similarity between the two cases.").

tent examiners and lower courts routinely reach inconsistent conclusions as to whether claim elements are adequately significant.

This type of indeterminacy hampers innovation. It drives up the cost and length of the patent application process and opens yet another front to be defended in patent litigation. Even more detrimentally, however, the continuing uncertainty over the classes of inventions that are eligible for patenting—and the specter that inventions that have been eligible for patenting for decades suddenly could become ineligible based on a newly minted assessment of "insignificance"—tends to discourage investment in potentially groundbreaking new technologies, which is exactly the "Progress of Science and the useful Arts" Section 101 is supposed to promote. *But see Bilski v. Kappos*, 130 S. Ct. at 3231 (inviting development of "limiting criteria that further the purposes of the Patent Act and are not inconsistent with its text").

If a proliferation of invalid patents is a problem, the solution is to be found in more robust enforcement of those provisions of the Patent Act that relate to patent invalidity—35 U.S.C. §§ 102, 103, 112. The solution is not to be found in constraining the subject matter eligible for patenting under Section 101. Unduly constraining the scope of patent-eligible subject matter—or leaving that scope subject to subjective analysis and the uncertainty that necessarily follows—risks hampering the development of new technologies in ways that are impossible to predict. That presents a threat to innovation and progress orders of magnitude greater than any threat that possibly could be occasioned by a decision that makes clear—as did *Diehr*—that concepts of novelty and nonobvi-

ousness have nothing whatsoever to do with patent eligibility under Section 101.

III. This Court's Early Patent-Eligibility Decisions Are Sufficient To Resolve Any Question Arising Under Section 101.

A. *Amici* respectfully submit that any additional "limiting criteria" for patent eligibility should not be drawn from the concept of "token post-solution activity," but instead return to this Court's earlier patent-eligibility precedents, which are the foundation upon which *Flook*, *Diehr*, and *Bilski* all rest.

Those cases determined an invention's eligibility for patenting by inquiring whether the claimed invention is a practical application of a new idea or a claim upon the idea itself. *See, e.g.*, *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end."); *Mackay Radio*, 306 U.S. at 94 ("While a scientific truth, or the mathematical expression of it, is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be."). Under this test, a process is eligible for patenting if it uses one or more disclosed physical things to produce a practical result or effect in the physical world; and is ineligible when it is untethered to a practical application. *See Cochrane*, 94 U.S. at 787-88 ("A process is a mode of treatment of certain materials to produce a given result.").

B. This broad standard can be traced back at least to *O'Reilly v. Morse*, which stated: "Whoever discovers that a *certain useful result* will be produced, in any art, machine, manufacture, or composition of matter, by the use of *certain means*, is entitled to a patent for it, provided he specifies the means." 56 U.S. (15 How.) 62, 119 (1854) (emphases added). In *Tilghman v. Proctor*, the Court repeated "this clear and exact summary of the law," which "affords the key to almost every case that can arise." 102 U.S. 707, 728 (1881).

Critically, this requirement that the claims be connected to the practical world has been effective in supporting the patent eligibility of new technologies, while preventing inventors from claiming the fundamental principles that underlie them, *i.e.*, from preempting a law of nature.

Thus, for example, when Samuel Morse claimed "the use of the motive power of the electric or galvanic current, which I call electro-magnetism, *however developed* for marking or printing intelligible characters, signs, or letters at any distances," he went beyond the bounds of patent eligibility. *O'Reilly*, 56 U.S. (15 How.) at 112 (emphasis added). In this, his eighth claim, Morse attempted to claim a useful result he surely achieved, but he declined to limit himself to any mechanism or method. This was fatal to the claim. *Id.* at 117 ("[Morse] has [discovered] a method by which intelligible marks or signs may be printed at a distance. And for the method or process thus discovered, he is entitled to a patent. But he has not discovered that the electro-magnetic current, used as motive power, in any other method, and with any other combination, will do as well.").

As the Court explained in *Tilghman*, the "eighth claim of Morse's patent was held to be invalid, because it was regarded by the Court as being not for a process, but for a mere principle." 102 U.S. at 726. The claim was ineligible because it sought to protect "the exclusive use of one of the powers of nature for a particular purpose." *Ibid.* Morse did not claim "any particular process for utilizing the power," but rather claim eight was "put forward on the ground that the patentee was the first to discover that it *could* be thus employed." *Id.* at 726-27. Notably, the *O'Reilly* Court allowed a number of other claims, including the fifth. 56 U.S. (15 How.) at 112. That claim was for "the system of signs, consisting of dots and spaces, and of dots, spaces and horizontal lines." *Id.* at 86. This system, an early version of Morse Code, was nothing other than a system for manipulating an on-off switch—the telegraph key—in a prescribed manner to produce the useful result of intelligible communications between two parties. And it was eligible for patenting as such.

C. A generation later this Court reaffirmed this distinction between useful process and principle in a case involving Alexander Graham Bell's telephone patent. "[E]lectricity, left to itself, will not do what is wanted. The art consists in so controlling the force as to make it accomplish the purpose." *The Telephone Cases*, 126 U.S. 1, 532 (1888). The Court drew the line even more finely than in *O'Reilly*, approving Bell's patent not for a method tied to a working apparatus (indeed, Bell's actual device did not yet work when he applied for the patent (*id.* at 535)), but instead on the manner of manipulating electricity to render it capable of transmitting voice. "[Bell] found out that, by changing the intensity of a continuous current so as to make it correspond exactly with the

changes in the density of air caused by sonorous vibrations, vocal and other sounds could be transmitted and heard at a distance. This was the thing to be done, and Bell discovered the way of doing it." *Id.* at 538-39. "Bell's patent is not alone for the particular apparatus he describes, but for the process that apparatus was designed to bring into use." *Id.* at 540.

The telling difference between Morse's ineligible eighth claim and Bell's claim was that Bell's patent claimed the process of altering a specified thing, an electrical current, to make it useful. Morse's claim, on the other hand, purported to cover all uses of electro-magnetism to obtain the claimed result. It provided no physical implementation; it merely described the abstract principle of using electromagnetism "however developed for marking or printing intelligible characters, signs, or letters, at any distances." *O'Reilly*, 56 U.S. (15 How.) at 112. Bell's claim consisted of an operative, specified process, while Morse's described only the objective of an unspecified process.

D. The notion of practical application in the physical world remains the touchstone of patent eligibility today. As this Court has consistently explained, "while an abstract idea, law of nature, or mathematical formula could not be patented, 'an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection.'" *Bilski v. Kappos*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 187) (emphasis added in *Bilski*).

It is important to recognize that the physical world includes much more than that which one can see or touch. It encompasses anything discernable or measurable, including (for example) electro-magnetic

signals propagated through the air, electric current transmitted by wire, electrostatic or magnetic charges encoded on computer media, or photonic impulses promulgated through a fiber optic cable. *See* John B. Anderson, *Digital Transmission Engineering* 1-5 (2d ed. 2005). Likewise, it includes the existence of a single molecule or chemical compound that is undetectable to the human eye but which when properly assayed could reveal practical information about the source of the molecule whether it be a chemical reaction or a human body. Even a process using a pair of atoms in a calculation by a quantum computer is a physical process used to produce a practical result or effect.

The implementation of a practical application to produce a "useful result" necessarily involves an alteration or manipulation of matter or energy. And claims directed to inventions possessing practical utility and producing useful results in the real world should be equally eligible for patenting whether or not they harness natural processes and forces to manipulate physical matter or physically embodied information. For centuries, machines and processes that have worked with or communicated physically embodied information or data have been considered patentable. Thus, for example, properly claimed computer-implemented processes use physical means to create useful results. Neither the Patent Act nor common sense suggests any reason why an analog filter—operating according to the principles of a mathematical algorithm—used to improve radio signals in a cellphone would be patent eligible and a

digital filter implemented on a general purpose processor using the same algorithm would not.[6]

A process that makes use of a disclosed thing, and produces a useful result in the physical world, does something more than describe an unpatentable principle—it is necessarily an application of that principle. Conversely, the more abstract a recited claim, the less likely it is a physical means or has a useful effect.

The dichotomy established in this Court's nineteenth-century decisions between principles and their application through physical means used to produce a useful result in the real world thus provides a clear, intuitive, and workable approach to determining patent eligibility and effectively implements this Court's prohibition on the patenting of abstract ideas. And it provides a more than adequate basis for assessing the eligibility of the claims at issue here.

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6 In a computer-implemented process the physical means consists primarily of the rapid activation and deactivation of millions of transistors to perform some useful function, such as displaying images and solving problems. *See generally* David A. Patterson & John L. Hennessy, *Computer Organization and Design* (4th ed. 2009). Such functions, implemented and made real, physical, and useful by the activity of transistors, are the manifestation of the process.

CONCLUSION

Subject-matter eligibility under 35 U.S.C. § 101 is the threshold inquiry for any applicant who seeks to patent his invention. Congress drafted that statute so that "anything under the sun that is made by man" would be eligible for a patent. The now-prevailing mode of Section 101 analysis that allows courts and the PTO to parse claims into the "underlying invention" and "extra-solution" elements based on inherently subjective evaluations of "significance," misplaced assessments of novelty, or both, is incompatible both with the statutory text and Congress's expressed intention. The Court, therefore, should reject that analytical framework. Instead, it should reaffirm the historical standard for patent eligibility of process inventions dating back to *O'Reilly v. Morse* and hold that a process invention is eligible for patenting if it uses "certain means" to create "a certain useful result."

Respectfully submitted.

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AMICUS CURIAE BRIEF

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

On Writ Of Certiorari
To The United States Court Of Appeals
For The Federal Circuit

BRIEF FOR MYRIAD GENETICS, INC., AS *AMICUS CURIAE* SUPPORTING RESPONDENT

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INTEREST OF *AMICUS CURIAE* [1]

Myriad Genetics, Inc. is a pioneer and world leader in the growing field of personalized medicine. Myriad's currently marketed personalized medicine products include innovative molecular diagnostic tests for diagnosing predisposition to disease (e.g., BRAC*Analysis*® testing assesses a woman's risk for breast and ovarian cancer); for optimizing a patient's therapy (e.g., OnDose® testing measures the levels of 5FU in a patient's blood so that dosing can be adjusted to deliver the right amount of drug for the individual patient); and for determining a patient's prognosis (e.g., PROLARIS® testing helps urologists determine a prostate cancer patient's risk of recurrence and disease-specific death). Myriad's products are now used by more than 40,000 healthcare providers in the United States in the care of their patients.

Myriad's past innovation and commercial success, as well as the patients whose lives are improved by our products, have benefited greatly from an appropriately strong U.S. patent system. In reliance on the prospect of continuing patent protection for its advances, Myriad is making substantial investment in research and development and working diligently to deliver the next generation of personalized medicine products. Myriad scientists analyze thousands of specimens, searching the human body's

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[1] All parties have consented in writing to the filing of this *amicus curiae* brief. No counsel for any party authored this brief in whole or in part, and no person or entity other than *amicus curiae*, their members, or counsel made a monetary contribution to the preparation or submission of this brief.

biochemicals (DNA, RNA, microRNA, proteins, and metabolites) to identify molecular markers that correlate with disease characters and drug response. Such correlations are key to Myriad's development of new products and methods, helping Myriad deliver the promise of personalized medicine in preventing diseases, optimizing disease treatment, improving lives, and reducing healthcare costs.

The massive investment in researching and developing these new products and methods would not be feasible for Myriad, or for any company, without the promise of patent protection for the resulting inventions. The cost of discovering, validating, and commercializing such personalized medicine products is significant. In the context of BRACAnalysis® testing alone, Myriad—

- has invested hundreds of millions of dollars in creating the innovative isolated BRCA1 and BRCA2 molecules, developing methods of using such molecules to detect predisposition to breast and ovarian cancer, and in establishing and refining its laboratory and data analysis processes to where they are now the gold standard;
- has invested well over $200 million in raising doctor and patient awareness of hereditary breast and ovarian cancer;
- employs a sales force of over 350 throughout the country to educate doctors on the power of genetic testing; and
- employs hundreds of skilled customer service, billing, and medical services personnel who help guide doctors and

patients through the testing and insurance reimbursement process.

This level of investment cannot possibly be made, and the resulting level of testing quality and patient access cannot possibly be maintained, absent strong patent protection, which allows a company a fair return on its investment in the inventive process.

Myriad thus has an interest in ensuring that patent claims to specific and practical diagnostic uses of correlations such as those in this case are affirmed as directed to patent-eligible subject matter. Absent such claims, there would not be adequate patent protection for future personalized medicine products, long-settled expectations would be upset, and the significant investment by Myriad and others in research and development would not be adequately incentivized. The important and developing industry of personalized medicine would be seriously jeopardized if such substantial and innovative contributions to science and medicine were denied patent protection at the doorway to the Patent Act, 35 U.S.C. § 101.

SUMMARY OF ARGUMENT

Personalized medicine uses molecular diagnostic tests to obtain information on a patient's genetic and molecular markers which are correlated to clinically useful disease characters. It holds enormous promise for significantly improving people's lives and reducing healthcare cost at each stage of patient care, including preventing disease by predicting which patients are at increased risk and improving disease outcomes by determining the best course of treatment (*e.g.*, the claims at issue in this case).

The significant investment and substantial risk involved in the innovation, development and delivery of personalized medicine products mandate strong patent protection. As with the pharmaceutical industry, personalized medicine relies on expensive and risky clinical studies to investigate, analyze, decipher, and confirm useful correlations between molecular markers and specific disease characters. Differences between pharmaceuticals and diagnostics, however, including a very different regulatory environment for molecular diagnostics, make broad patent coverage for the innovation underlying a diagnostic test critical.

In the post-Human Genome Project era, claims to diagnostic applications of such correlations may be the only meaningful claims available to adequately protect and incentivize the large investment needed to bring new and useful personalized medicine products to patients. Composition-of-matter claims, *e.g.*, isolated nucleic acids or proteins, may now be largely unavailable for patenting in light of the Human Genome Project. Claims like those at issue in this case, therefore, are particularly important

because they will be the only vehicle for introducing (and incentivizing) new and pathbreaking personalized medicine products for the public good.

Allowing such method patent claims to pass through the initial gateway to patentability will stimulate innovation. Numerous molecular markers can be correlated with each particular disease character. Patent claims to one diagnostic use of the correlation between a particular molecular marker and a specific disease character do not hinder, and actually drive, the innovations of other diagnostically useful correlations between other markers and that disease character for use in alternative diagnostic tests. Therefore, by allowing patent claims to practical diagnostic uses of specific correlations, the Constitutional purpose of the patent law is served and society reaps the benefits.

The Federal Circuit correctly found these claims patent-eligible under this Court's § 101 decisions, *e.g.*, *Diamond v. Diehr*, 450 U.S. 175 (1981), because they are directed to a specific and practical application of a personalized medicine correlation and not to the correlation *in the abstract*. Though it is no longer the exclusive test, the Federal Circuit also found an important clue to patent-eligibility in the fact that Prometheus's claims "necessarily involve" transformative steps.

Moreover, these claims do not pre-empt the basic tools of science. Indeed, these claims involve a technical aspect (*i.e.*, determining the level of a biomarker) *interacting* with the correlating step, which comports with the European approach to medical diagnosis process claims. In the words of *Diehr*, which harmonize well with the European

approach, such claims are patent-eligible because "they do not seek to pre-empt the use of [a correlation]. Rather, they seek only to foreclose from others the use of that [correlation] *in conjunction with* all of the other steps in their claimed process." *Diehr*, 450 U.S. at 187 (emphasis added).

The Prometheus claims ***as a whole*** are drawn to a specific and practical application of a personalized medicine correlation, rather than the correlation in the abstract, because they necessarily involve a transformation interacting *in conjunction with* the correlation. Personalized medicine method claims still have significant hurdles to clear under the other substantive sections of Title 35 (especially §§ 102, 103, and 112), and requirements of other areas of the law. But these methods are new and useful additions to the body of public knowledge that should, at minimum, be considered eligible for patent protection. They are certainly not so manifestly abstract that they should be barred at the gate by the coarse filter of § 101.

Amicus urges this Court to sustain a strong patent incentive to continue to protect important American investment in personalized medicine by affirming the patent-eligibility of molecular diagnostic method patent.

ARGUMENT

I. PERSONALIZED MEDICINE IMPROVES AND EXTENDS LIFE WHILE LOWERING HEALTHCARE COSTS BY CORRELATING MOLECULAR MARKERS TO CLINICALLY USEFUL DISEASE CHARACTERS

Personalized medicine uses diagnostic tests to obtain information on a patient's molecular markers (gene sequence variations, gene or protein expression levels, metabolites, etc.) that are associated with particular disease characters (*e.g.*, specific disease risk, presence or absence of disease, prognosis, response to particular drug therapies, etc.). Based on this information, preventive measures or tailored treatment regimens can be applied to the right patient at the right time and in the right amount.

The Human Genome Project ("HGP") heralded the dawn of the age of personalized medicine. With the completion of the HGP (and related projects), human genes have all been identified, and most genetic variations between individuals revealed. Such information has enabled further innovations utilizing the correlations between molecular markers and specific disease characters. These correlations are essential in developing molecular diagnostic products for use in personalized medicine.

Already, a number of personalized medicine products are widely used, exemplifying the current value and future promise of personalized medicine in improving quality of life and reducing costs.

One example is *Prometheus*'s product at issue in this case, which involves testing thiopurine levels in an autoimmune disease patient's blood to determine whether they are receiving an efficacious and

minimally toxic dose of a thiopurine-producing drug. The test is based on the correlation between a certain upper metabolite level and toxicity, on the one hand, and a certain lower metabolite level and lack of efficacy on the other. This enables doctors to optimize drug doses for individual patients.

An example of a widely available molecular diagnostic is HER_2 testing, which predicts a patient's response to the breast cancer drug Herceptin®. The test utilizes the correlation between HER_2 expression in a tumor and the tumor's predicated response to Herceptin®. Patients whose tumors overexpress (*i.e.*, overproduce) HER_2 show dramatic response to treatment with Herceptin® while patients whose tumors do not overexpress HER_2 show little or no benefit. Herceptin® costs over $50,000 a year and can cause severe side effects. *See* Bruce E. Hillner & Thomas J. Smith, *Do the Large Benefits Justify the Large Costs of Adjuvant Breast Cancer Trastuzumab?*, 25 J. Clinical Oncology 611, 612 (2007); Herceptin® Package Insert, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2000/trasgen020900LB.htm. Thus, a simple diagnostic test for HER_2 overexpression can spare a woman enormous cost and suffering if her tumor's biology indicates the drug will not work. *See generally*, Nandini Dendukuri et al., *Testing for HER_2-positive Breast Cancer: A Systematic Review and Cost-effectiveness Analysis*, 176 CAN. MED. ASS'N J. 1429 (2007).

More importantly, because treatment with an ineffective drug can erode part of a patient's window of opportunity for effective treatment, drug response tests such as the HER_2 test can help physicians and

patients make the right treatment decision at the right time. *See id.* Indeed, given the commonly low rate of drug efficacy in many medical fields,[2] there is a clear need for additional molecular diagnostic tests predicting a patient's response to many other drugs.

In prostate cancer, standard treatment in the U.S. is surgical resection of the prostate (prostatectomy) or radiation therapy. These aggressive treatments are expensive and the costs to the patient's quality of life can be severe (including incontinence and impotence). The unique characteristics of prostate cancer present newly diagnosed men with a challenging dilemma: treat, with all of the potential serious side effects, or roll the dice and engage in active surveillance. Prostate cancer is often slow growing, with a large percentage of diagnosed men never dying of the disease. Thus, unlike most other cancers, it is not a given that the benefits of treatment outweigh the risks for a man with prostate cancer. However, it is still cancer, and without the ability to determine indolent from aggressive cancer, most men choose to treat aggressively because it is potentially lethal.

Molecular diagnostic, pathological and histological tools, such as PSA measurements and Gleason scoring, are available to gauge prostate cancer aggressiveness. However, these techniques, especially measuring PSA, are notoriously inaccurate and subjective, and there is a serious unmet clinical

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[2] Selected major drugs are effective in 50% of rheumatoid arthritis, 30% of Alzheimer's, and 25% of cancer patients. Brian B. Spear *et al.*, *Clinical Application of Pharmacogenetics*, 7 TRENDS MOLECULAR MED. 201, 202 (2001).

need for more accurate, objective tools in prostate cancer prognosis.

After over four years of research and millions of dollars and counting in investment, *Amicus*'s researchers and academic collaborators recently demonstrated that the expression of genes associated with cell-cycle progression correlates with both prostate cancer recurrence and death. Jane Cuzik *et al.*, *Prognostic Value of An RNA Expression Signature Derived From Cell Cycle Proliferation Genes in Patients With Prostate Cancer: A Retrospective Study*, 12 LANCET ONCOL. 245, 255 (2011). The Prolaris® test is a patented molecular diagnostic assay that measures gene expression levels within a prostate tumor sample, derives a quantitative cell-cycle progression score ("CCP Score") from this information, and uses the CCP Score either independently or together with clinical parameters to predict the patient's risk of death. This knowledge can help men and their doctors decide whether to opt for aggressive treatment or active surveillance. In this way, Prolaris® promises to significantly improve prostate cancer treatment and help reduce unnecessary cost and suffering.

The BRAC*Analysis*® test commercialized by *Amicus* is a widely utilized personalized medicine product that predicts predisposition to hereditary breast and/or ovarian cancer. The test is based on the isolation and characterization of the *BRCA1* and *BRCA2* DNA molecules, done by *Amicus* and its collaborators in the mid-1990s. Women testing positive for a BRCA mutation can have up to a 92 percent risk of developing breast or ovarian cancer, or both, by age 70. *See* D. Ford *et al.*, *Genetic*

Heterogeneity and Penetrance Analysis of the BRCA1 and BRCA2 Genes in Breast Cancer Families, 62 AM. J. HUM. GENETICS 676, 682, Table 5 (1998). Additionally, mutation carriers previously diagnosed with cancer have a significantly increased risk of developing a second cancer.

For the BRAC*Analysis*® test, patients who meet certain criteria (*e.g.*, family history of cancer) are identified and the patients' *BRCA1* and *BRCA2* genes are analyzed for mutations in a clinical laboratory. If a cancer-predisposing mutation is found, preventive measures such as chemoprevention therapy and prophylactic surgery can be taken to avoid the suffering and treatment costs associated with cancer. Alternatively, increased surveillance can be adopted to detect cancer at an early, more treatable stage. BRAC*Analysis*® is proven to improve quality and duration of life and reduces lifetime healthcare costs. *See* Kristin Anderson *et al.*, *Cost-effectiveness of Preventive Strategies for Women with a BRCA1 or a BRCA2 Mutation*, 144 ANNALS INTERNAL MED. 397, 397 (2006) ("[C]ost-effective policies on [BRAC*Analysis*®] testing and preventive treatment options may save up to $800 million of the more than $8 billion or more spent each year on breast cancer diagnosis, prevention, and treatment."). Due to the efforts and investment of *Amicus* in test development and physician and patient education, over 400,000 women have been tested and have received critical information that can be used to make life-saving decisions.

These are just a handful of products that illustrate personalized medicine's potential. Indeed, personalized medicine is often touted as one of the

promising solutions to the current crisis in our healthcare system. *See* Personalized Medicine Coalition, *The Case for Personalized Medicine* at 4-6, *available at* http://www.personalizedmedicinecoalition.org/sites/default/files/TheCaseforPersonalizedMedicine_5_5_09.pdf (last visited Nov. 4, 2011).

II. THE PERSONALIZED MEDICINE INDUSTRY IS BUILT ON THE SETTLED EXPECTATIONS OF THE INCENTIVE PROVIDED BY STRONG PATENT PROTECTION FOR CLAIMS TO DIAGNOSTIC USE OF CORRELATIONS

A basic understanding of challenges in the personalized medicine industry shows that patents in general, and patents claiming diagnostic use of correlations in particular, are vital to its full emergence and continued viability.

A. As in the Pharmaceutical Industry, Strong Patent Rights Are Needed to Ensure Recovery of the Substantial Investment Required to Fund Research, Development, and Product Delivery in Personalized Medicine

Much like in the pharmaceutical industry, personalized medicine research and development are extremely costly and offer a very low rate of success. *See generally*, Jim Kling, *Diagnosis or Drug? Will Pharmaceutical Companies or Diagnostics Manufacturers Earn More from Personalized Medicine?*, 8 EMBO REP. 903 (2007). Primary among these barriers to entry are the cost and difficulty of innovation and validation. *See, e.g.*, Christopher B. Granger *et al.*, *National Heart, Lung, and Blood Institute Clinical Proteomics Working Group Report*,

109 CIRCULATION 1697, 1700 (2004). A typical discovery study requires hundreds or thousands of carefully selected patient samples, each having expertly collected clinical information. After generating data on thousands or tens of thousands of molecular markers from these samples, scientists must then sift through millions of data points in hopes of discovering a statistically significant correlation between one or more of these markers and a particular disease character.

The amount of time and effort required is enormous. Additional clinical trials are required to demonstrate the clinical utility of the discovered correlation. Many trials are essentially equivalent to pharmaceutical trials in both design and scope, sometimes involving following patients for years to determine long-term survival. Costs for research tools such as reagents and laboratory equipment (especially high-throughput platform equipment such as microarray chips) can also be substantial, especially since many of these reagents and platforms are themselves patented products. For example, researchers at Genomic Health reportedly spent well over 100 million dollars and 7 years, including numerous clinical studies involving hundreds of patients, in bringing Onco*Type* DX® to market.[3]

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[3] Department of Health & Human Services, *Personalized Health Care: Pioneers, Partnerships, Progress*, 84 (2008), *available at* http://www.hhs.gov/myhealthcare/news/phc_2008_report.pdf. Onco*Type* DX® determines a breast cancer patient's risk of recurrence after surgery based on the correlation between the expression levels of selected genes in tumor and the likelihood of cancer recurrence.

Even after such significant time and capital outlays, success is not guaranteed; failures far outnumber successes. Again there are clear parallels to the drug industry, where many drugs that were successful in a phase II clinical trial inexplicably fail in a larger phase III trial. Similarly, many personalized medicine products with promising results in a small discovery study will fail to show any predictive value in a larger validation study.

While personalized medicine shares many of the challenges of the pharmaceutical industry, it is also adversely affected by the differences. Despite the similar costs and barriers to success between pharmaceuticals and molecular diagnostics, personalized medicine ironically promises investors an inherently smaller potential payoff compared to pharmaceuticals for the very same reason it reduces aggregate healthcare costs. Personalized medicine testing is often a one-time event—*i.e.*, the test determines once and for all whether a patient will respond to a particular treatment. Pharmaceutical products, on the other hand, often have "repeat" customers taking a daily dose for a very long time.

Another key challenge in personalized medicine (as compared to pharmaceuticals), which calls for broader patent protection in personalized medicine, is the regulatory environment. Laboratory-developed personalized medicine products presently are not FDA-regulated and are instead subject to CLIA certification for the technical aspects of the clinical laboratory where the test is performed. This is a significant difference. For pharmaceuticals, narrow patent coverage of the specific compound marketed by the innovator company is typically sufficient. This

is because any company hoping to market a competitive drug must either market the identical compound (and thus infringe even a very narrow patent claim covering only the innovator's specific compound) or undertake its own expensive clinical trials. This choice provides a significant barrier to entry in pharmaceuticals. For molecular diagnostics, however, broader patent coverage is required because there is no regulatory framework that puts would-be generic diagnostic providers to the difficult choice required of would-be generic drug marketers. Someone looking to offer a competing diagnostic test may make trivial changes to the innovator's diagnostic process, piggyback on the innovator's clinical studies, and merely validate the technical aspects of the laboratory to satisfy CLIA requirements. Unlike in pharmaceuticals, broad claims are needed to prevent easy circumvention of the patents protecting the significant investment in a new and useful personalized medicine product.

Even greater than the cost of innovation and validation of such personalized medicine products is the cost of actually delivering them to patients. *Amicus*'s BRAC*Analysis*® testing is an excellent example. *Amicus* has invested hundreds of millions of dollars in raising doctor and patient awareness of hereditary breast and ovarian cancer and in building the technical and personnel infrastructure to deliver genetic testing of the highest quality to over 700,000 patients.

The reason investors, both private and public, have been willing to pour such huge sums of capital into such risky ventures is the settled expectation that limited exclusivity will provide for a reasonable

return. *Amicus* urges this Court to tread very carefully when asked, as by the petitioner in this case, to upset those expectations. *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 799 (2002) ("[C]ourts must be cautious before adopting changes that disrupt the settled expectations of the inventing community." (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997))).

B. Claims to Diagnostic Use of Correlations Such as Those in Prometheus's Patents Are Usually the Only Patent Claims Available That Can Provide Meaningful Protection for Personalized Medicine Products

> The § 101 patent-eligibility inquiry is only a threshold test. Even if an invention qualifies as a process, machine, manufacture, or composition of matter, in order to receive the Patent Act's protection the claimed invention must also satisfy 'the conditions and requirements of this title.' § 101. Those requirements include that the invention be novel, *see* § 102, nonobvious, *see* § 103, and fully and particularly described, *see* § 112.

Bilski v. Kappos, 130 S. Ct. 3218, 3225 (2010). Personalized medicine patents face significant challenges under the "conditions and requirements" of Title 35 beyond the initial one of § 101.[4] These

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[4] One challenge facing personalized medicine claims, which is made worse by a restrictive reading of § 101, is so-called "divided infringement." Narrowing application of § 101 in personalized medicine is forcing many applicants to settle for patent claims that are exceedingly easy to circumvent by splitting up the laboratory process and data analysis portions of

other provisions give ample, and better-calibrated opportunities to sift out undeserving patent claims. While the Human Genome Project ("HGP") has provided a boon to personalized medicine by greatly facilitating the discovery of important correlations, it has simultaneously made patenting in personalized medicine much more challenging, because human genes (including most genetic variations) have been elucidated and virtually all proteins encoded by these genes are now known to the public.

Claims to new techniques for analyzing molecular markers may still be available, but this does not solve the problem of incentivizing personalized medicine products. The development and manufacture of diagnostic tools is a wholly distinct industry that services the molecular diagnostic industry.

(continued...)

the typical personalized medicine process. William L. Warren & Lei Fang, Biotechnology Patent Validity in Jeopardy, GENETIC ENGINEERING NEWS: LEGAL AFFAIRS, Oct. 1, 2010 *available at* http://www.genengnews.com/gen-articles/biotechnology-patent-validity-in-jeopardy/3421/ (last accessed Nov. 4, 2011) ("To the extent that diagnostic method claims involve only mental correlative steps, they are at risk for being characterized as merely an unpatentable 'abstract idea.' On the other hand, for claims that involve multiple steps of the medical continuum, in order to capture a more clearly patentable transformation step along with the diagnostic mental correlation step, it is more likely that a single entity will not infringe the claim, precluding any remedy."); *see also Akamai Techs., Inc. v. Limelight Networks, Inc.*, 629 F.3d 1311 (Fed. Cir. 2010), *rehearing en banc granted*, 419 F. App'x 989 (Fed. Cir. 2011); *McKesson Techs. Inc. v. Epic Sys. Corp.*, 98 U.S.P.Q.2d 1281 (Fed. Cir. 2011), *rehearing en banc granted*, 2011 WL 2173401 (Fed. Cir. May 26, 2011).

Patenting of new tools or techniques does nothing to incentivize the discovery of new correlations and the development of the use of such correlations into commercial personalized medicine products. Invalidation of a claimed method for the diagnostic use of correlations—particularly at the threshold of the Patent Act—threatens to destroy the personalized medicine industry in its infancy.

III. THE FEDERAL CIRCUIT CORRECTLY RULED THAT THE PROMETHEUS CLAIMS ARE PATENT-ELIGIBLE UNDER 35 U.S.C. § 101 BECAUSE THEY ARE NOT DRAWN TO AN ABSTRACT IDEA OR LAW OF NATURE *PER SE*

Section 101 of the Patent Act broadly mandates that a patent may be obtained for "*any* new and useful process, machine, manufacture, or composition of matter." 35 U.S.C. § 101 (2006) (emphasis added). The use of the expansive "any" as well as the legislative history of the Patent Act have led the Court to interpret the scope of patent-eligible subject matter broadly. *Diehr*, 450 U.S. at 182. Of course, there are limits to § 101. *See id.* at 185 ("Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas."); *see also Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584 (1978). Nevertheless, such judicially created exclusions must be narrowly applied, for "Congress intended statutory subject matter to 'include anything under the sun that is made by man.'" *Diehr*, 450 U.S. at 182 (citing S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., Sec. 2d Sess., 6 (1952)).

A. The Prometheus Claims Do Not Claim a Fundamental Principle in the Abstract but Instead Claim a Specific and Practical Application of a Personalized Medicine Correlation

If a claimed process is an *application* of a law of nature, natural phenomenon or abstract idea, the process is patent-eligible. *Diehr*, 450 U.S. at 187. For example, while this Court has repeatedly explained that "Einstein could not patent his celebrated law that $E = mc^2$; nor could Newton have patented the law of gravity," *id.* at 185 (citing *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)), the Court has explicitly upheld a patent claiming a specific and practical application of the law of gravity. *Eibel Process Co. v. Minn. & Ont. Paper Co.*, 261 U.S. 45, 64-65 (1923). However, "[a]n idea *of itself* is not patentable." *Diehr*, 450 U.S. at 185 (citing *Rubber-Tip Pencil Co. v. Howard*, 87 U.S. (20 Wall.) 498, 507 (1874) (emphasis added). Thus, "when a claim recites a mathematical formula (or scientific principle or phenomenon of nature), an inquiry must be made into whether the claim is seeking patent protection *for that formula in the abstract*."[5] *Id.* at 450 U.S. at 191 (citing *Benson*, 409 U.S. 63 (1972)) (emphasis added).

All inventions originate as an "abstract idea" and all processes employ some "physical phenomenon"

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[5] The American Heritage® Dictionary of the English Language, defines "abstract" as withdrawn or considered apart from concrete existence; not applied or practical; theoretical. "Abstract." THE AMERICAN HERITAGE® DICTIONARY OF THE ENGLISH LANGUAGE 8 (3d ed. 1992).

and embody some "law of nature." *Diehr*, 450 U.S. at 189 n.12 ("To accept the analysis proffered by the petitioner would, if carried to its extreme, make all inventions unpatentable because all inventions can be reduced to underlying principles of nature which, once known, make their implementation obvious."); *Funk Bros. Seed Co. v. Kalo Co.*, 333 U.S. 127, 135 (1948) (Frankfurter, J., concurring) ("Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent."). The real question is whether the patent *claim* is directed to an idea or law of nature *in the abstract* or whether the claim recites *a practical application* of that idea or law. *Diehr*, 450 U.S. at 187; *id.* at 191; *Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 868 (Fed. Cir. 2010) ("[T]he Supreme Court in *Bilski* refocused this court's inquiry into processes on the question of whether the subject matter of the invention is abstract"). This is hardly a binary question. Instead courts are tasked with deciding where a claimed invention falls along the continuum between a purely abstract idea or law and a clearly practical process.

Judge Learned Hand's "levels of abstraction" analysis in copyright may provide a helpful framework, by analogy, for deciding whether a patent claim is directed to an abstract idea or law of nature.[6] *Nichols v. Universal Pictures Corp.*, 45 F.2d 119 (2d

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[6] This Court has often used patent principles in analyzing copyright cases, and *vice versa*. *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2067 (2011) (citing *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913 (2005)); *eBay Inc. v. MercExchange LLC*, 547 U.S. 388 (2006).

Cir. 1930). In *Nichols*, Judge Hand was faced with a claim that one play infringed a copyright held on another play. Judge Hand reached his decision of no infringement by breaking the two works down into a "series of abstractions," with the highest levels of abstraction being unprotectable as representing "ideas." *Id.* at 121 ("otherwise the playwright could prevent the use of his 'ideas,' to which, apart from their expression, his property is never extended"). He noted that themes shared between the two plays were shared with innumerable other creative works and "no more susceptible of copyright than the outline of Romeo and Juliet." *Id.* at 122. In language strikingly similar to that used by this Court in giving examples of laws of nature that cannot be patented, Judge Hand explained that "[t]hese would be [...] as little capable of monopoly as *Einstein's Doctrine of Relativity*, or Darwin's theory of the Origin of Species." *Id.* at 121 (emphasis added); *accord Chakrabarty*, 447 U.S. at 309.

Here, no one has rigorously identified the "abstract idea" or "law of nature" supposedly being preempted, *per se*. At the highest level of abstraction, the abstract idea at issue could be stated as follows: "Efficacy and toxicity of most drugs are dose-dependent, such that exposure to a drug below a certain level will lead to lower than desired efficacy and exposure above a certain other level will result in greater than desired toxicity." No one alleges, and with good reason, that Prometheus's claims are directed to this idea (or law) *per se*. However, it is helpful to take a step back and, following Judge Hand's analysis in *Nichols*, consider what lies at the clearly "abstract" end of the spectrum, since only the highest levels of abstractness should be barred from

patenting by § 101. *Research Corp.*, 627 F.3d at 868 ("[T]his court also will not presume to define 'abstract' beyond the recognition that this disqualifying characteristic should exhibit itself so manifestly as to override the broad statutory categories of eligible subject matter and the statutory context that directs primary attention on the patentability criteria of the rest of the Patent Act.").

Personalized medicine claims such as Prometheus's are often summarized as being directed to "(1) obtain[ing] test results and (2) think[ing] about them." *Lab. Corp. of Am. Holdings v. Metabolite Labs.*, 548 U.S. 124, 136 (2006) (Breyer, J., dissenting); Pet. Br. i (Prometheus's claim "covers observed correlations between blood test results and patient health"). This is slightly more concrete than the abstract idea stated above and, if Prometheus had claimed at this level of abstraction (*e.g.*, a process for determining response comprising measuring *any* metabolite levels in a patient and thinking about the results), such a claim would still likely be patent-ineligible.

This shortcut—of boiling a claim down to its "gist"—is not only improper under this Court's precedent, but it also seriously mischaracterizes the actual process claimed here. *Compare* Pet. Br. i ("a patent claim that covers observed correlations between blood test results and patient health") *with Diehr*, 450 U.S. at 188-89 ("It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis."). One need merely glance at *the claims themselves* to see that they are not so broad and abstract as to cover *any* act of testing for *any*

metabolite and then thinking about it. "[T]he claims recite *specific* treatment steps, not just the correlations themselves. And the steps involve a *particular* application of the natural correlations: the treatment of a *specific* disease by administering *specific* drugs and measuring *specific* metabolites." *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1355 (Fed. Cir. 2010) ("*Prometheus II*") (emphasis added).

The familiar pair of cases of *Flook* and *Diehr* help to further illustrate the continuum from abstractness to patent-eligibility. Flook's patent failed because it attempted to claim a mathematical formula for updating alarm limits *in the abstract*. *Diehr*, 450 U.S. at 191. "An 'alarm limit' is *simply a number*, and the Court concluded that the application sought to *protect a formula* for computing this number." *Diehr*, 450 U.S. at 186 (emphasis added). The patentee in *Flook* included post-solution steps (*e.g.*, replacing the old number with the number newly produced) as well as a field-of-use limitation (in processes "comprising the catalytic chemical conversion of hydrocarbons") in the claims. *Flook*, 437 U.S. at 589-90.

The Court, however, saw such post-solution steps and field-of-use limitations as illusory since neither the claims nor the specification gave any teaching on how the formula was especially suited to the process or even on how the formula might be used in such a process. *Diehr*, 450 U.S. at 186. The patent application did not explain how the variables used in the formula were to be selected, nor did the application "contain any disclosure relating to the chemical processes at work, the monitoring of process

variables, or the means of setting off an alarm or adjusting an alarm system. *All that it provides is a formula* for computing an updated alarm limit." *Diehr*, 450 U.S. at 186-87 (citing *Flook*, 437 U.S. at 586) (footnote omitted) (emphasis added). In other words, the claims were patent-ineligible because they were an example of "[a] competent draftsman [...] attach[ing] some form of post-solution activity to [a] mathematical formula." *Flook*, 437 U.S. at 590.

In contrast, the claims in *Diehr* were directed to a process for curing rubber that made use of a mathematical formula. The patents and claims recited detailed information on the process for curing rubber, how the formula was applied in the process, and how the process variables were measured and calculated. *Diehr*, 450 U.S. at 178-79. Rather than a thinly veiled attempt to claim a mathematical formula *per se*, the claims in *Diehr* were clearly directed to an industrial process that used a formula in a beneficial way. *Id.*

The Prometheus claims are unlike the *Flook* claims and similar to the *Diehr* claims on every relevant point identified by the Court. Claim 46 is representative. Unlike *Flook*, Claim 46 does not seek to claim any natural law or phenomenon or idea *in the abstract* because: (1) the preamble and "wherein" clauses of Claim 46 impose meaningful limits by restricting it to a *specific* and practical application of the correlation (low level of abstraction); and (2) the specification includes detailed teachings on how the underlying correlation is specifically suited to use in the fields specified in the claims (more *Diehr* than *Flook*). *Prometheus II*, 628 F.3d at 1355.

B. The Prometheus Claims Are Patent-Eligible Because They "Necessarily Involve" a Machine or Transformation "In Conjunction With" a Correlation Step

Moving beyond *Flook* and *Diehr*, the Prometheus claims are patent-eligible because they necessarily involve a machine or transformation. *Prometheus II*, 628 F.3d at 1357. While this Court recently held that the "machine-or-transformation test" is not the exclusive test for patent-eligibility, the Court acknowledged that it is a "useful clue." *Bilski*, 130 S. Ct. at 3227.

The Federal Circuit found that the step of "determining the level of 6-thioguanine" in Claim 46 of the '623 patent "necessarily involves" the use of devices ("machines"), chemical reagents ("compositions of matter") and the transformation of patient samples. *Prometheus II*, 628 F.3d at 1357. These physical transformations recite defined test subjects (a subject having an "immune-mediated gastrointestinal disorder") and specific factors that are tested ("level of 6-thioguanine"). Finally, the test data generated by the claimed process "clearly represent physical and tangible objects," i.e., the concentrations of analytes, and are in fact transformed when applied to the correlation. *In re Bilski*, 545 F.3d 943, 962-63 (Fed. Cir. 2008) (en banc) (discussing *In re Abele*, 684 F.2d 902 (C.C.P.A. 1982)). The application of such test data to the correlations recited in the claims for diagnostic purposes is a specific, practical application of these correlations. The claims *as a whole* recite a specific, practical and tangible application of the correlation.

Petitioner urges this Court to follow Justice Breyer's dissenting opinion in *LabCorp* by dissecting Prometheus's claims into two steps: "(1) obtain test results and (2) think about them," and then disregarding the first (transformative) step for § 101 purposes simply because that test step is in the prior art. *LabCorp*, 548 U.S. at 137 (Breyer, J., dissenting); Pet. Br. 37. However, this analysis clearly violates *Diehr*'s firm admonition that, for § 101 purposes, the claim "must be considered *as a whole*. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Diehr*, 450 U.S. at 188, 189 n.12, 193 n.15.

Petitioner's and the *LabCorp* dissent's dissection of the claims is doubly questionable because the transformations in the claims are necessary and "central to the purpose of the claimed process." *Prometheus II*, 628 F.3d at 1355 (quoting *Bilski*, 545 F.3d at 962). There can be no therapeutic optimization without the "determining" step. *Id.* at 1357. The determining and correlating steps work "in conjunction" to accomplish the diagnosis. *See Diehr*, 450 U.S. at 187 (finding patent-eligible a process that "admittedly employs a well-known mathematical equation" because the patentee did not "seek to pre-empt the use of that equation" but rather "only to foreclose from others the use of that equation *in conjunction with* all of the other steps in their claimed process.") (emphasis added).

C. This Court Has Repeatedly Stated That a Claim to a Process Need Not Explicitly Recite a Transformative Step to Be Patent-Eligible

While the Prometheus claims appear to explicitly recite a "transformation," *Amicus* urges this Court to reaffirm that they need not. As a plurality of this Court recognized in *Bilski*, much modern scientific and technological advancement involves the assembly and transmission of newly generated knowledge, including "advanced diagnostic medicine techniques." *Bilski*, 130 S. Ct. at 3227. Thus, it should not matter for purposes of patent-eligibility under § 101 whether the Federal Circuit in *Prometheus* construed the patent claims to require the physical process of measuring metabolite levels in a sample, or to necessarily involve such a physical measurement (*i.e.*, as a preceding step not explicitly recited but still necessary before any "determining" can be done). Certainly, the word "determining" does not *per se* imply any physical act of measuring, as this term is often used to refer to mental activities.[7] This ambiguity has unfortunately led some to interpret both *Prometheus* decisions as holding that *explicit* recitation of a physical transformation is *required* for patent-eligibility, when this Court in *Bilski* held that

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[7] *Compare Prometheus II*, 628 F.3d at 1357 ("Prometheus's asserted claims recite transformative [...] 'determining' steps") *with In re Bilski*, 545 F.3d at 962-63 (discussing the CAT scan of *In re Abele*, with no clearly recited physical transformation, as meeting the machine-or-transformation test). The Federal Circuit in *Bilski* and *Abele* held that transforming data was sufficient to be a "transformation" and for patent-eligibility, so long as the data had some clear nexus to and represented something tangible. *In re Abele*, 684 F.2d at 908.

even the machine-or-transformation test was not the exclusive inquiry for § 101 patent-eligibility.

In so holding, this Court in *Bilski* repeated what it said in *Flook:* "[A] valid process patent may issue even if it does not meet [the machine-or-transformation test]." 130 S. Ct. at 3227 (quoting *Flook*, 437 U.S., at 588, n. 9); *accord Benson*, 409 U.S. at 71; *In re Abele*, 684 F.2d at 908. Even if they are not explicitly recited as required physical steps in the claimed process, the fact that these physically transformative activities must inherently take place before the claimed method can be practiced is sufficient to remove the claimed subject matter from the "abstract" realm and place it squarely in the real world of patent eligibility.

D. Looking for a Transformation, Explicitly Recited or Not, Interacting with a Correlation Accords with the European Approach and Will Incentivize Critical Domestic Investment

Under the European Patent Convention, discoveries, scientific theories and mathematical methods are excluded from the scope of patentable subject matter. *Eur. Pat. Conv.*, Art. 52(2)(a) (2000). In EPO G1/04, the European Patent Office Enlarged Board of Appeal considered whether a diagnostic method claim that includes a step of "purely intellectual exercise" falls within the scope of patent-eligible subject matter under the European Patent Convention. *See EPO* G1/04, p.19-20.[8] The Board

[8] The Enlarged Board characterized a typical medical diagnosis method to "include (i) the examination phase involving the collection of data, (ii) the comparison of these data with

held that "[t]he subject-matter of a claim including technical and non-technical features may satisfy the requirements of Article 52(1) EPC [predecessor to EPC 2000 Article 52(2)(a)] if the non-technical features interact with the technical features in order to bring about a technical effect." *EPO* G1/04, p.19 (citation omitted). This "interaction" rule resonates well with the notion of "in conjunction with" in *Diehr* and is easily workable. *Diehr*, 450 U.S. at 187. Under this rule, European patents have been routinely granted on medical diagnosis method claims like those at issue in this case. *See, e.g.*, *EPO* T310/99.

Failure to protect medical diagnosis claims similarly in the United States threatens to put the U.S. at a competitive disadvantage. *Bilski*, 130 S. Ct. at 3227 (expressing concern over "uncertainty as to the patentability of [...] advanced diagnostic medicine techniques" and other "inventions in the Information Age"). This disadvantage "is not theory but history." *Classen Immunotherapies, Inc. v. Biogen Idec*, Nos. 2006-1634 & 2006-1649, 2011 U.S. App. LEXIS 18126, at *49 (Fed. Cir. Aug. 31, 2011) (Rader, J., additional views). In "Additional views" reminiscent of Justice Frankfurter's prediction that "[a]rguments drawn from such terms [as 'laws of nature' ...] could fairly

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(continued...)

standard values, (iii) the finding of any significant deviation, *i.e.* a symptom, during the comparison, and (iv) the attribution of the deviation to a particular clinical picture, *i.e.* the deductive medical or veterinary decision phase." *EPO* G1/04, p.18. The last step, *i.e.* the deductive medical decision phase, is often an intellectual exercise, and is of a non-technical nature. *Id.* at 19.

be employed to challenge almost every patent," *Funk Bros.*, 333 U.S. at 135 (Frankfurter, J., concurring), Judge Rader bemoaned "a rising number of challenges under 35 U.S.C. § 101." 2011 U.S. App. LEXIS 18126, at *45. However, the problem goes far beyond wasting judicial resources:

> In the past, this cause-effect relationship of eligibility restrictions and stifling innovation favored our country in, for example, biotechnology[,where,. . .] with some considerable blame on its eligibility doctrines, Europe lost innovation investment to the United States [and o]ur country became the world leader in biotechnology innovation.

Id. at 49, 50. Judge Rader's ominous warning has the very real potential of coming true for personalized medicine depending on the outcome of this case: "Nevertheless, the tide can turn against us, too." *Id.*

E. A Time-Limited Patent Monopoly On a Particular Diagnostic Use of a Particular Correlation Does Not Wholly Pre-empt that Correlation

One oft-cited concern over claims directed to fundamental principles in the abstract is that such claims "pre-empt" all uses of that principle. *Diehr*, 450 U.S. at 187; Pet. Br. i ("the patent effectively preempts use of the naturally occurring correlations"). Some worry that such claims would block all use of the basic tools of invention and innovation, which should be made freely accessible to promote technological advances. *See Benson*, 409 U.S. at 67; *see also LabCorp*, 548 U.S. at 128 (Breyer, J., dissenting). Though this may be a valid concern in

some cases, it simply does not apply to personalized medicine claims such as Prometheus's.

Properly limited personalized-medicine method claims such as these do not preclude the public from using the recited correlations for other purposes or from finding analogous correlations using the same analytes. *Prometheus II*, 628 F.3d at 1355 ("The Supreme Court's decision in *Bilski* did not undermine our preemption analysis of Prometheus's claims[, which] do not [...] preempt natural correlations"). Prometheus did not attempt to claim the abstract idea of correlating drug metabolite levels to efficacy or toxicity. Instead these claims are directed to using a very specific correlation for "optimizing [...] treatment of an immune mediated gastrointestinal disorder" and do not preclude the public from any other uses of the correlation, such as for optimizing therapeutic efficacy of 6-thioguanine-providing drugs (*e.g.*, 6-mercaptopurine and azathioprine) for treatment of leukemia[9] or kidney transplantation rejection.

Nor do they pre-empt the use of the correlation (1) for studying the correlation itself, *e.g.*, the mechanisms underlying the drug toxicity or efficacy; (2) for determining the types and degree of toxicity; or (3) for developing alternative genetic tests for predicting a patient's response to 6-thioguanine-

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[9] 6-Mercaptopurine is approved by the FDA as Purinethol® for treating acute lymphatic leukemia. *See* FDA, *MedWatch: The FDA Safety Information and Adverse Event Reporting Program*, *available at* http://www.fda.gov/medwatch/SAFETY/2004/jul_PI/Purinethol_PI.pdf.

providing drugs. Through these diagnostic process claims, patentees are granted—in exchange for bringing these discoveries to the public as a whole—a time-limited, exclusive right to the concrete use of a particular correlation for the diagnosis of a particular medical condition. Nothing more.

Unlike Einstein's $E=mc^2$ and Newton's law of gravity, the correlations in medical diagnosis process claims such as the Prometheus claims have a qualitatively narrower spectrum of applicability, and thus exert much less impact on upstream scientific and technological research. Far from granting a monopoly on "basic tools" of a fundamental or upstream nature, such claims grant relatively narrow exclusivity over a downstream research endpoint that has matured into a process that is ready to be marketed for the benefit of the public.

F. Because There Are Numerous Possible Correlations for a Particular Disease Character, a Patent on a Particular Diagnostic Use of a Particular Correlation Incentivizes Scientists to Discover New Correlations and Develop Better Personalized Medicine Products

These patent claims do not "interfere with, or discourage, development and the further spread of useful knowledge," *LabCorp*, 548 U.S. at 128 (Breyer, J., dissenting). Rather, they stimulate innovation, create competition and spur the further spread of useful knowledge. *See State Indus., Inc. v. A.O. Smith Corp.*, 751 F.2d 1226, 1236 (Fed. Cir. 1985) ("One of the benefits of a patent system is its so-called 'negative incentive' to 'design around' a competitor's products, even when they are patented,

thus bringing a steady flow of innovations to the marketplace."); Peter Lee, *Patents, Paradigm Shifts, and Progress in Biomedical Science*, 114 YALE L.J. 659, 686-88 (2004). A basic understanding of molecular biology shows that personalized medicine is no exception to, and in fact exemplifies, this principle.

In the human body, all biological components—from individual genes to small molecules, proteins, cells, tissues and entire organs—work together through an array of interconnected biological pathways that facilitate communication among genes, molecules, and cells, to accomplish biological functions and properties of life (*i.e.*, response to stimuli, reproduction, growth and development, and maintenance of homeostasis). *See* National Institutes of Health, *Building Blocks, Biological Pathways, and Networks, available at* http://nihroadmap.nih. gov/buildingblocks/ (last visited Nov. 4, 2011). Each pathway may be comprised of thousands of macromolecules interacting with and influencing each other as well as members of other pathways. When functioning properly, these pathways maintain the human body as a dynamic but stable unit.

Disturbance of any one member of a pathway may lead to changes in not only other members of the same pathway but also members of other pathways, resulting in a disease or disorder. Likewise, a single disease or disorder can be associated with numerous changes in many pathways. *See generally*, Ali Torkamani *et al.*, *Pathway Analysis of Seven Common Diseases Assessed by Genome-Wide Association*, 92 GENOMICS 265 (2008). Therefore,

there can be numerous biomarkers correlating with a particular disease. Indeed, the primary goals of research and development in the field of personalized medicine are to discover such correlations and biomarkers and to use these to develop molecular diagnostic tests.

With so many possible correlations to the same disease, a patent monopoly on a particular diagnostic use of a particular correlation between one biomarker and a particular disease would not preclude scientists from discovering other, potentially better correlations between other biomarkers and the same disease. Just as in pharmaceuticals there are seemingly endless variations on a chemical compound that will still target the same enzyme (sometimes even better than the original compound), there are nearly infinite possible correlation combinations between biomarkers and diseases. As an illustration, more than four patented diagnostic tests, beside Onco*type* DX®, are currently commercially available for the same diagnostic purpose: Predicting a breast cancer patient's benefit from chemotherapy as well as her risk of recurrence. *See* Jeffrey S. Ross *et al.*, *Commericalized Multigene Predictors of Clinical Outcome for Breast Cancer*, 13 ONCOLOGIST 477 (2008). Other tests for the same diagnostic purposes are still being developed. *Id.*

When claims drawn to the use of a particular correlation for diagnosing a particular medical condition are made patent-eligible, the roadblock of such patent claims, together with the roadmap of the disclosure required to get a patent, will actually stimulate scientists to discover new correlations that can be used to design better diagnostic tests for the

same medical condition. As such, the Constitutional purpose of the patent law is served and society reaps the benefits. *See* Lee, 114 YALE L. J. at 686-88.

CONCLUSION

The decision of the Federal Circuit should be affirmed.

Respectfully submitted.

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEF

No. 10-1150

In The
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(d/b/a Mayo Medical Laboratories)
and MAYO CLINIC ROCHESTER,

Petitioners,

vs.

PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ Of Certiorari To The United States Court Of Appeals For The Federal Circuit

BRIEF OF *AMICUS CURIAE* NATIONAL VENTURE CAPITAL ASSOCIATION IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICUS CURIAE*[1]

The National Venture Capital Association (NVCA), with more than 400 members, is the venture community's preeminent trade association, advocating for policies that encourage innovation and reward long-term investment. NVCA's mission is to foster greater understanding of the importance of venture capital to the U.S. economy and support entrepreneurial activity and innovation. Venture capitalists are committed to funding America's most cutting-edge entrepreneurs, working closely with them to transform breakthrough ideas into emerging growth companies that drive U.S. job creation and economic growth. According to a 2011 Global Insight study, venture-backed companies accounted for nearly 12 million jobs and $3.1 trillion in revenue in the United States in 2010.

NVCA and its members have an interest in preserving patent rights that have brought life-saving innovations to market and spurred economic growth and continued scientific advancement.

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[1] No counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than *amicus curiae*, its members, or its counsel made a monetary contribution to its preparation or submission. The parties have consented to the filing of this brief.

SUMMARY OF ARGUMENT

The venture capital industry has made possible some of the most important technological advancements in the last several decades. Its willingness to assume great risks and invest in companies like Genentech helped establish the biotechnology industry, an industry which, year after year, provides hundreds of thousands of jobs, generates billions of dollars in revenue, and makes available to the general public countless life-saving innovations. *See* Ernst & Young, *Beyond Borders, Global Biotechnology Report* 39 (2011) ("*Beyond Borders*").

This industry is in the process of a paradigm shift into the burgeoning field of personalized medicine – the tailoring of medical treatment to the individual characteristics of each patient. Personalized medicine enables treatment decisions to be made based on biological markers that signal an individual's susceptibility to certain diseases, the efficacy of particular treatments, and patient prognosis. The use of diagnostic correlations to select customized therapies is the foundation of personalized medicine and results in more focused and cost-efficient healthcare. Consequently, personalized medicine holds the promise of improved patient care and disease prevention, health care cost savings, and increased medical product development. *See* President's Council of Advisors on Science and Technology, *Priorities for Personalized Medicine* 7-8 (2008) ("PCAST *Priorities*").

But realizing the promise of personalized medicine – like many other healthcare advancements – is an undertaking mired by long development timelines, government regulations, uncertain industry adoption, and a complex healthcare reimbursement system. This process can cost hundreds of millions of dollars and take several years before any return on investment is realized. HHS, *Personalized Health Care: Pioneers, Partnerships, Progress* 132 (2008) ("HHS *Personalized Health Care*"). Venture capitalists, however, have historically been able to take on such long-term risk because patent protection in the underlying technology guarantees potentially large rewards if a product can be brought to market.

Removing patent eligibility for diagnostic correlations removes this incentive and jeopardizes the billions of dollars venture firms have already invested in personalized medicine companies in reliance on patent protection. It further removes incentives for future investment in this emerging market, threatening to halt an industry and deprive the public of the associated benefits of targeted cost-effective medical care, job creation, and economic growth.

This Court's jurisprudence on patentable subject matter simply does not support upsetting the established structure. Patents covering specific diagnostic correlations do not entirely preempt laws of nature. As broad patent eligibility has facilitated this country's continued innovative leadership, consistent with the constitutional mandate "to promote the progress

of science and useful arts," this Court should affirm the Federal Circuit's ruling in favor of Respondent.

ARGUMENT

I. REALIZING THE PROMISE OF PERSONALIZED MEDICINE REQUIRES PATENT PROTECTION.

A. Patents Enable Venture Capital Investment in Personalized Medicine

1. Challenges Facing the Personalized Medicine Industry

Continued advances in genomics and molecular biology – most notably the sequencing of the human genome – has uncovered biological markers correlated with the presence of disease, susceptibility to disease, and particular responses to known treatment regimes. PCAST *Priorities* at 1, 7. Markers like these can be used to develop new diagnostic tests. The tests will enable physicians to confirm disease, tailor dosing regimens to individual variations in metabolic response, and prescribe individualized treatment plans. Diagnostic correlations can also be used to develop new therapeutics targeted at physiological consequences of a patient's specific genetic profile. *Id.* at 1. We are thus entering the age of personalized medicine.

Much excitement surrounds personalized medicine because of the disruptive nature of the innovation.

It does not merely provide incremental improvement to known technologies, it has the potential of permanently transforming the way we practice medicine and the entire healthcare industry. Instead of relying on the traditional trial-and-error approach to diagnosis and treatment, personalized medicine will enable more efficient diagnosis and targeted treatment. It will enable the recognition and treatment of disease even before symptoms appear, and it will identify predisposition to disease allowing for more effective preventative action. HHS *Personalized Health Care* at 10.

The result: improved quality of care and reduced healthcare costs. Most drugs prescribed are effective in fewer than 60 percent of treated patients. *Id.* at 9. Personalized medicine can identify patients in advance who will not need certain treatments or will suffer dangerous side effects. It can also lead to and accelerate the development of new treatments. Not only can new targeted therapeutics be developed, but the regulatory approval process can be streamlined by identifying and narrowing appropriate patient subpopulations for clinical trials. PCAST *Priorities* at 8.

As of 2009, the market for personalized medicine was $232 billion estimated to double to $452 billion by 2015. PricewaterhouseCoopers, *The New Science of Personalized Medicine: Translating the Promise into Practice* 13 (2009) ("PwC *Personalized Medicine*"). The core segment of diagnostic tests and targeted therapeutics was $24 billion, with an estimated

10 percent annual growth rate. But the anticipated growth and the promise of personalized medicin do not come easily. As with all disruptive innovations, the path to personalized medicine is uncharted and uncertain. Transforming awareness of molecular markers into validated and accepted diagnostics and therapeutics available to the general public is a long, arduous, and unpredictable process.

Significant obstacles stand in the way of personalized medicine. Research and development in this field is expensive and challenging. Tens of millions of dollars are needed to tackle the methodological and logistical challenges to validating apparent correlations between genetic markers and diseases. Translating voluminous genomic data into concrete diagnostic correlations requires sufficient sample sizes, quality control in the underlying DNA sampling, a rigorous statistical approach to analyzing data, and a consistent standard across the industry. PCAST *Priorities* at 29-30. This is a time-consuming process that requires careful review of data and significant coordination among multiple different industry players.

There are additionally significant hurdles in the regulatory and reimbursement systems. While the eventual hope is a streamlined approach for regulatory approval for targeted diagnostics and therapeutics, the current system is not designed to accommodate new complex genomics-based diagnostics. Regulatory guidelines are ambiguous or incomplete with respect to defining risks associated

with new diagnostics, designing standards for studying performance of these diagnostics, and labeling and regulation of therapeutics intended for use with diagnostics. *Id.* at 41. There is also the practical necessity of convincing insurance companies, Medicare, and Medicaid to pay for these new tests, which requires robust evidence supporting the safety and efficacy of products. *Id.* at 45-48.

Even if a company successfully overcomes the scientific and regulatory hurdles set before it, market success requires adoption by the patient and physician community. *Id.* at 9. Thus, even after the several years and tens of millions of dollars spent in R&D and the regulatory process, more time and money must be spent educating the public and establishing new medical standards of care.

Talented scientists and entrepreneurs willing to invest the time and energy to bring this exciting new technology to market will need to find significant sources of capital to overcome each of these challenges.

2. The Role of Patents and Venture Capital in Overcoming Challenges in Personalized Medicine

In the face of these obstacles and the need for tens, if not hundreds, of millions of dollars in capital, emerging personalized medicine companies do not have access to traditional avenues of funding. These companies simply would not exist without venture

capital, often the only source of funding for high-risk disruptive innovations like personalized medicine. NVCA, *Patient Capital: How Venture Capital Investment Drives Revolutionary Medical Innovation* 7 (2007) ("*Patient Capital*") ("Young life sciences companies are dependent on venture capital investors to grow their business. Because their capital needs are so large and their path to market so long and risky, it is difficult for life sciences startups to access bank financing or other more traditional sources of capital.").

Over the past decade, venture capitalists have invested over $25 billion annually, mostly in disruptive technologies. Global Insight, *Venture Impact, The Economic Importance of Venture Capital-Backed Companies to the U.S. Economy* at 5 (2011) ("*Venture Impact*"). Approximately one-third of their investments will fail, however. *Id.* at 11. With such a high failure rate, venture investment is economically feasible only if the venture-backed companies that do succeed generate significant enough rewards. This is especially true with biotechnology, where the failure rates are particularly high due to the risks associated with development and regulatory approval.

Consequently, patent protection – which promises market exclusivity – is crucial to the success of personalized medicine companies. PCAST *Priorities* at 21 ("The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical

products, including genomics-based molecular diagnostics."); *Patient Capital* at 12 ("No other industry is as dependent on developing and protecting intellectual property as the life sciences industry.").

Patent protection enables companies to attract venture funding. In fact, many venture firms employ professionals with direct expertise to review investment candidates, subjecting a company's patents – pending and issued – to extensive review before investing. Schneider, Judith E., *Intellectual property: The driving force for growth and funding*, 8 Journal of Commercial Biotechnology 320, 324 (2002); *see also* Barfield, Claude, et al., *Biotechnology and the Patent System* 11 (2007) ("Investors believe that in order for the biotechnology sector to succeed, it is critical that biotechnology firms be able to obtain and enforce strong patents.").

Such due diligence into a company's patent portfolio is compelled by economic necessity. A significantly higher percentage of venture capital backed companies that have succeeded (i.e., been acquired or gone public) have patent portfolios compared to those that have gone out of business. Hadzima, Joseph, et al., *IP in early state commercial and investment success*, Intellectual Assert Management 52, 55 (March/April 2010). Patent portfolios are of particular value in the healthcare industry, as opposed to the information technology sector, for example. *Id.* Indeed, in biotechnology, strong patent protection correlates with the amount of R&D investments made

by companies, and weak patent laws engender poor investment in R&D, diminishing a company's probability of success. Grabowski, Henry, *Patents, Innovation and Access to New Pharmaceuticals*, 5(5) J. Int'l Econ. Law 849, 854 (2002).

With all the other uncertainties that exist in the personalized medicine industry, patents are needed to counterbalance the extremely high risk faced by startup companies. The lack of patent protection discourages venture investment, and will leave the promise of personalized medicine unrealized. *See* Graham, Stuart J.H., et al., *High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey*, 24:4 Berkeley Tech. L. J. 1255, 1279 (2009) (venture-backed firms are much more likely to hold patents and venture-capital investors appear much less willing to fund companies that don't hold patents).

B. Venture Capital Investment Backed by Patent Protection Leads to Important Life-Saving Innovations

The importance of patents to personalized medicine and the general public is not merely theoretical. Because patent protection has thus far been allowed for diagnostic correlations, venture capitalists have invested hundreds of millions of dollars in personalized medicine companies. As a result, revolutionary new medical diagnostics focused on improved treatment for cardiovascular disease, cancer, and diabetes

– among the leading causes of death in the United States – are now available to the public.

The Corus® CAD test offered by CardioDx, Inc. is one of these new diagnostics. Made available in 2009, Corus CAD is a blood test that measures the expression level of 23 genes to assess a patient's risk of coronary artery disease (CAD). Diagnosis of CAD traditionally requires a coronary angiogram – an x-ray procedure requiring insertion of a catheter into the femoral artery or jugular vein. Over two million coronary angiograms are performed each year, but 30 percent of them turn out normal. With Corus CAD, using just a blood test, physicians can better identify the 30 percent who do not need angiograms, patients can avoid unnecessary procedures and radiation exposure, and healthcare payers can avoid a major expense category.

Making Corus CAD widely available to the public has been a long and expensive process that continues to this day. Founded in 2004, CardioDx has been able to secure significant venture financing over the years. Armed with patent applications[2] covering the diagnostic correlations between gene expression levels and coronary artery disease underlying Corus CAD, CardioDx has attracted over $150 million in

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[2] *See* U.S. App. No. 12/682,579 (Pub. No. US2011/0184712), "Predictive Models and Methods for Diagnosing and Assessing Coronary Artery Disease," and U.S. App. No. 12/816,232 (Pub. No. US2011/0015865), "Determination of Coronary Artery Disease Risk."

venture capital financing in the last two years alone. These funds have been used to secure regulatory certification for CardioDx's clinical laboratories. They have funded multi-center trials proving the efficacy and utility of Corus CAD. *See generally* Rosenberg, Steven, et al., *Multicenter Validation of the Diagnostic Accuracy of a Blood-Based Gene Expression Test for Assessing Obstructive Coronary Artery Disease in Nondiabetic Patients*, 153:7 Ann. Internal Med. 425-434 (2010). And they have been used to educate the physician and patient community on the proper use of benefits of Corus CAD. CardioDx is now using its latest round of financing, $40 million secured in May 2011, to reach out to payors to secure reimbursement for use of the test. *See* Press Release, Mohr Davidow (May 11, 2011), available at http://www.mdv.com/press-room/press-releases/cardiodx-completes-60-million-equity-financing. These efforts – made possible by venture funding secured by patent protection – have not gone unrecognized. Corus CAD was named one of Time Magazine's Top 10 Medical Breakthroughs of 2010 and was a recipient of the Wall Street Journal's Technology Innovation Awards in 2010.

The Onco*type* DX® assay from Genomic Health, Inc. is another personalized diagnostic made possible by venture capital investment. Founded in 2000, Genomic Health secured $30 million in venture funding before its Onco*type* DX assay was made available in 2004. The Onco*type* DX assay predicts the likelihood that certain breast cancer patients will experience a recurrence within 10 years by measuring the

expression levels of 21 different genes and providing a personalized estimate of the risk of recurrence for each patient. The scores help physicians identify the low-risk patients who will not likely benefit from additional chemotherapy. The ability to make these assessments translates to substantial cost savings to the healthcare system and spares many patients the unnecessary disruption, suffering, and toxic effects of chemotherapy.

The validation of Onco*type* DX genes, selected from thousands of potential genes, was the product of thousands of hours of research made possible by venture investment. *See* Brief of Amici Curiae in Support of Defendants' Opposition to Plaintiffs' Motion for Summary Judgment filed in *Association of Molecular Pathology v. United States Patent and Trademark Office*, Case No. 09-cv-4515, United States District Court of the Southern District of New York, Dkt. # 197 at 3 ("Genomic Health Amicus"). The ability to maintain patents covering Genomic Health's work and the specific Onco*type* DX gene correlations[3] was crucial for attracting and maintaining the interest of the venture capital community. *Id.* Their investments supported years of research and development,

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[3] *See, e.g.*, U.S. Patent No. 7,081,340, "Gene Expression Profiling in Biopsied Tumor Tissues"; U.S. Patent No. 7,056,674, "Prediction of Likelihood of Cancer Recurrence"; U.S. Patent No. 7,569,345, "Gene Expression Markers for Breast Cancer Prognosis"; U.S. Patent No. 7,526,387, "Expression Profiling Algorithm and Test for Cancer Prognosis."

numerous validation studies, and regulatory approval for Genomic Health's clinical laboratories – which ultimately enabled commercial use of Onco*type* DX. *See generally* Genomic Health, Corporate History available at http://www.genomichealth.com/en-US/Company/History.aspx ("Genomic Health History"). They enabled Genomic Health to spend time and money introducing Onco*type* DX to the physician community, constructing economic models demonstrating the cost-effectiveness of the product, and securing accreditation by the College of American Pathologists. *Id*. As a result, Genomic Health had a successful initial public offering in 2005. Since then, the Onco*type* DX breast cancer assay has been recommended in both the American Society of Clinical Oncology and National Comprehensive Cancer Network clinical practice guidelines. Genomic Health Amicus at 3. In 2006, Genomic Health also secured Medicare reimbursement for Onco*type* DX. *See* Genomic Health History. With its success, Genomic Health continues to support research and clinical studies in oncology by reinvesting approximately $1.4 million in collaborative research and providing over $1 million in free services to independent researchers using Onco*type* DX. Genomic Health Amicus 3-4.

PreDx® Diabetes Risk Score was introduced in 2008 by Tethys Biosciences, a company committed to reducing the clinical and economic burden of preventable diseases by preempting their onset. PreDx DRS is a simple fasting blood test that measures biomarkers correlated with development of type 2

diabetes. Diabetes afflicts over 27 million people in the United States and is the seventh leading cause of death. A patient's PreDx risk score enables physicians to identify patients with high risk of developing diabetes and prescribe appropriate preventative care to ward off disease onset. In addition to the obvious medical benefits for patients, PreDx DRS reduces the necessity and cost of future procedures for the treatment of diabetes. *See* Sullivan, Sean D., et al., *Cost Effectiveness of Risk Stratification for Preventing Type 2 Diabetes Using a Multi-marker Diabetes Risk Score*, 14:5 Journal of Medical Economics 609-616 (2011).

Tethys Bioscience has secured patent protection for PreDx DRS covering the correlation of measured proteins in the blood with risk of diabetes and has a portfolio that includes numerous other patent applications.[4] As a result, since 2008, Tethys Bioscience has secured over $100 million in venture capital investments which it continues to invest in the development of diagnostics for assessing risk of heart attack, osteoporotic fractures, and cardiometabolic diseases. For its work, Tethys Bioscience was selected as 2012 Technology Pioneer by the World Economic Forum for Innovative Diagnostics.

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[4] Tethys Bioscience, Inc. has a patent portfolio that includes at least 7 published patent applications and 1 issued patent, U.S. Patent No. 7,723,050, "Diabetes-related biomarkers and methods of use thereof."

These are just three examples of the type of innovation and advancements in existence because of patent protection and venture capital investments. Over the past 20 years, the venture community has actually invested $15 billion in more than 2000 deals specializing in cardiovascular disease, $14.7 billion in approximately 1600 deals focused on combating cancer, and close to $5 billion in almost 600 deals for the treatment of diabetes. *Patient Capital* at 5. In 2008 alone, venture capitalists invested over $2.7 billion in almost 250 startups focused on human bioscience. PwC *Personalized Medicine* at 15. The potential benefit that may come from this level of investment is immeasurable. Denying patent protection now not only forfeits the billions of dollars currently invested, but jeopardizes the technologies that the investments were intended to bring to market.

C. Denying Patent Protection Threatens the Far-Reaching Benefits Made Possible by Venture Capital Investments

Facilitating venture investment through patent protection not only makes the direct healthcare benefits provided by companies like CardioDx, Genomic Health, and Tethys Bioscience possible, it is responsible for far-reaching downstream economic benefits as well.

While venture capital investments equal less than 0.2 percent of the US GDP, annually, VC-backed companies have generated revenue equal to 21 percent of

the US GDP. *Venture Impact* at 2. Venture-backed companies constituted 11 percent of private sector jobs in 2010. *Id.* at 3. The biopharmaceutical industry, for instance, has an enormous ripple effect throughout the economy. The Milken Institute projects that for every job within biopharmaceuticals, an additional 6.7 jobs are created in other sectors of the economy. *Patient Capital* at 8, *citing* Milken Institute, *Biopharmaceutical Industry Contributions to State and U.S. Economies* (2004).

Venture capital's investment in new, cutting-edge high growth companies means that it plays a leading role in creating new industries which hold the potential unfettered job and revenue growth. Cutting off incentives for venture investment in personalized medicine would eliminate a sector of venture-backed biotechnology companies. Venture-backed companies represent 74 percent of biotechnology jobs and 80 percent of biotechnology revenue. *Venture Impact* at 9. That's over 400,000 jobs and $161 million in revenue in 2010. *Id.* A reduction of these jobs and the revenues generated by eliminating venture-backed personalized medicine companies will have significant unintended consequences on the economy. Indeed, venture-backed companies have been sustaining the economy, outperforming the total overall economy in 2009-2010. *Id.* at 2. Where overall revenues decreased 1.5 percent, venture-backed revenue grew 1.6 percent, totaling $3.1 trillion in 2010 (10 percent of total U.S. sales).

Moreover, as was the case with Genomic Health, venture-backed companies that succeed and go public often re-invest in and support new and further advances. These advances go on to feed the cycle of innovation, job creation, and revenue growth. Thus, the current system has supported steady economic growth and support for new technologies and emerging industries. There is simply no policy reason to disturb the status quo.

The suggestion that patents stifle innovation by discouraging or prohibiting basic research does not comport with reality. In practice, patents have a negligible effect on research, in part because ground-level scientists are not aware of patents and because ultimately their research pursuits are driven primarily by scientific importance or interests regardless of patents. Walsh, John P., *Patents, Material Transfers, and Access to Research Inputs in Biomedical Research*, Final Report to the National Academy of Sciences' Committee Intellectual Property Rights in Genomic and Protein-Related Inventions 2, 6, 13 (2005). Indeed, it has been found that "few of the frictions [caused by patents] that had been anticipated had materialized," and that "patents on research tools did not impede biomedical research as feared." *Id.* at 6. Thus, in reality, there does not exist any evidence of the feared negative effects of patents on further research. What does exist, however, is the undeniable importance of patents to the entire U.S. economy in general, and the future of personalized medicine in particular.

II. PATENTING DIAGNOSTIC CORRELATIONS DOES NOT PREEMPT ALL USE OF A NATURAL PHENOMENON.

There is no need to risk the future of personalized medicine and the health of the economy. The diagnostic correlations that have already been granted patent protection (like the one covered by Respondent's patents), and those for which personalized medicine companies and researchers are seeking patents, fall within the scope of patentable subject matter. Neither Respondent nor the personalized medicine industry is trying to patent "laws of nature." Rather, what is being patented are very specific complex interrelationships between a multitude of biological markers and their correlation with specific diseases. Identifying the relevant set of biological markers, characterizing their contribution to disease, and developing clinically validated diagnostics based on those correlations is the product of human innovation. Patenting such work does not preempt nature; there are infinite combinations of biological markers that can be studied and possibly correlated with any number of diseases. Others are free to do that work, and indeed, patent protection would incentivize them to do so.

Thus, Petitioner's argument that a patent covering a diagnostic correlation – in this case, "the biological correlations between metabolite levels and health" – preempts all use of that natural phenomenon does not hold water. The argument depends on

characterizing the relevant natural phenomenon with an inappropriately high level of specificity.

Petitioner's analytic approach presupposes that in determining patent eligibility of diagnostic correlations, the relevant natural phenomena should be defined as the specific correlation being claimed. If that tautology were accepted, no diagnostic correlation could ever be patentable. Indeed, taken to its logical extreme, nothing would be patent eligible – all patents preempt the scope of their claims.

As this Court has noted, the "subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 315 (1980). Thus, the exceptions to patent eligibility for "laws of nature, natural phenomena, and abstract ideas," should be used sparingly to deny patentability only in the clearest cases. *See Association for Molecular Pathology v. United States Patent and Trademark Office*, 653 F.3d 1329, 1374 (Fed. Cir. 2011) (Moore concurring in part) ("the judiciary is ill-suited to determine whether the claims at issue promote or inhibit science and useful arts in all but the clearest cases").

This is not one of those clear cases warranting denial of patent eligibility. Instead, Petitioner seeks to use a judicially created exception to deny patent eligibility to an entire class of patents directed to biological correlations. This court has previously avoided

such categorical approaches to analyzing patentability, warning of their "wide-ranging and unforeseen impact." *Bilski v. Kappos*, 130 S. Ct. 3218, 3229 (2010). A ruling that would deny patentability to diagnostic correlations would certainly have negative wide-ranging impact on personalized medicine, current economic incentives, and the overall health of the economy.

CONCLUSION

For the foregoing reasons, the judgment of the Court of Appeals should be affirmed.

Respectfully submitted,

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES)
AND MAYO CLINIC ROCHESTER,

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v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

ON WRIT OF CERTIORARI TO THE
UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF OF NEW YORK INTELLECTUAL PROPERTY LAW ASSOCIATION AS *AMICUS CURIAE* IN SUPPORT OF NEITHER PARTY

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A. Claimed Inventions Must Be Directed to One of the Four Statutory Categories of Patent-Eligible Subject Matter: Process, Machine, Manufacture, or Composition of Matter 7

B. Claimed Inventions Directed to Fundamental Principles—"Laws of Nature, Physical Phenomena, or Abstract Ideas"—Are Not Eligible for Patent Protection But Practical Applications of Fundamental Principles Are Patent-Eligible 9

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INTEREST OF *AMICUS CURIAE*[1]

The New York Intellectual Property Law Association ("NYIPLA") respectfully submits this brief *amicus curiae* in support of neither party.[2] NYIPLA is professional association of more than 1,500 attorneys whose interests and practices lie in the area of patent, copyright, trademark, trade secret and other intellectual property law.

NYIPLA members include a diverse array of attorneys specializing in patent law, from in-house counsel for businesses that own, enforce and challenge patents, to attorneys in private practice who represent inventors in various proceedings before the United States Patent and Trademark Office. A substantial percentage of NYIPLA attorneys participate actively in patent litigation, representing both patent owners and accused infringers. NYIPLA members frequently engage in

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[1] Pursuant to Rule 37.6, no counsel for a party authored this brief in whole or in part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than NYIPLA, its members, or its counsel made a monetary contribution to its preparation or submission.

[2] Petitioners and Respondent have consented to the filing of briefs in support of either party or neither party in docket entries dated August 8 and 4, 2011, respectively.

patent licensing matters, representing both patent licensors and licensees.

NYIPLA's interest in this case stems from the suggestion in the patent law community that the Court may use this case as a vehicle for creating one or more strict categories of patent-ineligible subject matter under 35 U.S.C. § 101. The activities of NYIPLA members and practitioners depend on the consistently-applied and longstanding broad scope of patentable subject matter under the Patent Act. As a result, members have a strong interest in ensuring that the Court does not disturb the current clearly-defined framework governing the patentability of inventions that Congress set forth in the Patent Act and this Court has construed in its decisions.

NYIPLA expressly declines to take a position on whether the patent claims at issue in this case meet all of the statutory conditions of patentability. With that caveat in mind, however, NYIPLA respectfully submits that the Court should reaffirm its long-held conclusion that the scope of patent-eligible subject matter under 35 U.S.C. § 101 is extremely broad, encompasses any invention claiming a statutory class of patentable subject matter, and excludes only claims directed to laws of nature, physical phenomena and abstract ideas.

Regardless of the Court's ultimate decision on the questions the parties presented, NYIPLA urges the Court to reaffirm the rules governing the threshold patentability inquiry, synthesized in *Diehr*

and reaffirmed in *Bilski*, as those rules are clear, readily-implemented, and should not be disturbed.

SUMMARY OF ARGUMENT

After more than two decades of silence on the issue of patent eligibility under 35 U.S.C. § 101, this Court considered important principles relating to patent eligibility last year in *Bilski v. Kappos*, 561 U.S. __, 130 S.Ct. 3218 (2010).

Significantly, *Bilski* reaffirmed the general principles and inquiries that govern patent eligibility under Section 101, first synthesized in *Diamond v. Diehr*, 450 U.S. 175 (1981). Specifically, the Court has adhered to and consistently applied an inquiry based on two questions:

1. Does the claimed subject matter fall within one of the four statutory categories of patent-eligible subject matter: (i) process, (ii) machine, (iii) manufacture or (iv) composition of matter (or any improvement thereof)?

2. Is the claimed subject matter directed to one of three so-called "fundamental principles," *i.e.*, laws of nature, natural phenomena, or abstract ideas?

See Bilski, 130 S. Ct. at 3225; *Diehr*, 450 U.S. at 185 (citing, *inter alia*, *Gottschalk v. Benson*, 409 U.S. 63,

67 (1972) and *Parker v. Flook*, 437 U.S. 584, 589 (1978)).

Though the second question assures that a patent cannot claim a fundamental principle, this Court has long recognized that, as discussed in *Diehr* and *Bilski* and tracing its roots to hoary precedent, a patent claim may nonetheless be directed to the practical application of a fundamental principle (such as a method of curing rubber that uses a known algorithm).

This Court has developed more than two centuries of jurisprudence relating to what the Federal Circuit calls the "machine-or-transformation" test, a "useful tool" to determine whether a particular claim is directed to a fundamental principle or simply claims a practical application of a fundamental principle. In *Bilski*, the Court rejected the notion that the machine-or-transformation test was the sole or exclusive test to answer this question. Nonetheless, the Court recognized that the test remains a "useful tool" in the patentable subject matter eligibility analysis.

The Court should continue to apply these broad guidelines in determining patent eligibility. But NYIPLA respectfully submits that in order for the machine-or-transformation test to remain a useful tool, the Section 101 inquiry must end when the test is *met*. Other sections of the Patent Act establishing conditions of patentability—novelty, non-obviousness and sufficient disclosure—should

instead dictate whether a valid claim may issue. Unless a claim that meets the machine-or-transformation test is *de facto* patent-eligible, the test cannot be a useful tool. Put another way, satisfying the machine-or-transformation test should create a safe harbor of patent-eligible subject matter. But, of course, as a non-exclusive test, if a patent claim does *not* meet the machine-or-transformation test, continued analysis may be necessary to see if the patent claims a fundamental principle or simply a practical application of a fundamental principle.

Finally, NYIPLA emphasizes the vital role patents play in the United States economy. Patents—when appropriately awarded—encourage innovation and transparency, and advance the Constitutional goal of "promot[ing] the Progress of Science and useful Arts." U.S. Const., art. I, § 8, cl.8. This Court should resist the temptation to bow to an outspoken minority who would undermine a patent system that our founding fathers thought was so important that they included it in Article I of the Constitution and enacted it into one of its earliest public laws. NYIPLA respectfully submits that this Court should reaffirm the broad scope of patent-eligible subject matter under Section 101.

ARGUMENT

The statutory language of 35 U.S.C. § 101 clearly defines patent-eligible subject matter:

> Whoever invents or discovers any new or useful process, machine, manufacture or composition of matter, or any new or useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101. Almost forty years of the Court's detailed interpretation confirms the breadth of the statute. In *Bilski v. Kappos*, the Court once again "decline[d] to impose limitations on the Patent Act that are inconsistent with the Act's text," 130 S.Ct. at 3231, and reconfirmed the wide scope for patentability of inventions under Section 101. *Id.* at 3225; *see J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130 (2001); *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980); ("As this Court recognized over 20 years ago in *Chakrabarty*, the language of § 101 is extremely broad.") (citation omitted).

NYIPLA submits that nothing about the case at bar compels any reevaluation of the straightforward rules for assessing patent eligibility, that, when applied consistently, enable inventors,

practitioners and the public alike to determine with reasonable certainty whether an invention is patentable under Section 101.

I. THE COURT SHOULD REAFFIRM THE WELL-SETTLED GENERAL PRINCIPLES GOVERNING PATENT-ELIGIBLE INVENTIONS UNDER 35 U.S.C. § 101

The Court has repeatedly referred to patentability under Section 101 as a "threshold" analysis, *e.g.*, *Diehr*, 450 U.S. at 188, that is assessed before other conditions and requirements of patentability are considered. *Bilski*, 130 S.Ct. at 3225. This threshold analysis raises two questions, each discussed below, that are necessary to determine whether an invention is directed to patent-eligible subject matter. *See id.*

A. Claimed Inventions Must Be Directed to One of the Four Statutory Categories of Patent-Eligible Subject Matter: Process, Machine, Manufacture, or Composition of Matter

Section 101 broadly states that "any" subject matter in the four independent categories of invention—process, machine, manufacture or composition of matter—qualify for protection. 35 U.S.C. § 101. The Court reemphasized the comprehensive scope of those categories in *Bilski*,

stating that "Congress took this permissive approach to patentability to ensure that ingenuity should receive a liberal encouragement." *Bilski*, 130 S.Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 308-09 (quoting 5 Writings of Thomas Jefferson 75-76 (H. Washington ed. 1871)) internal quotation marks omitted)).

Since its amendment in 1952, the Patent Act has expressly provided that an inventor may obtain a patent covering a process, "subject to the conditions and requirements of this title." 35 U.S.C. § 101. Congress defined "process" in an expansive manner: "process, art, or method, and includes a new use of a known process, machine, manufacture, composition of matter or material." 35 U.S.C. § 100(b); *see Flook*, 437 U.S. at 588 n.9 (observing that the "statutory definition of 'process' is broad").

In *Bilski*, the Court refused to adopt a new rule categorically excluding patent-eligible subject matter from the term "process." *Bilski*, 130 S.Ct. at 3227 ("Section 101 is a 'dynamic provision designed to encompass new and unforeseen inventions.'") (quoting *J.E.M. Ag Supply*, 534 U.S. at 135; *Charkrabarty*, 447 U.S. at 308 (cautioning that "courts should not read into the patent laws limitations and conditions which the legislature has not expressed") (internal quotation and citation omitted)).

Though NYIPLA takes no position on whether the invention at issue claims patent-eligible subject

matter, there is no reason for the Court to turn away from its prior rulings by imposing potentially unworkable limitations on the word "process" to restrict subject matter eligibility.

B. Claimed Inventions Directed to Fundamental Principles—"Laws of Nature, Physical Phenomena, or Abstract Ideas"—Are Not Eligible for Patent Protection But Practical Applications of Fundamental Principles Are Patent-Eligible

Congress specifically intended that patentable subject matter "include anything under the sun that is made by man." *Chakrabarty*, 447 U.S. at 309 (quotation and citation omitted). In *Chakrabarty*, however, the Court specifically excluded "laws of nature, physical phenomena, and abstract ideas" from patent-eligible subject matter under § 101. *Id.* at 313; *see also Bilski*, 130 S.Ct. at 3226; *Diehr*, 450 U.S. at 185; *Flook*, 437 U.S. at 588-89; *Benson*, 409 U.S. at 67 ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes."); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

Abstract natural principles are excluded from patentable subject matter primarily because knowledge discovered by mere observation of the natural world has not been "applied to some practical purpose" in a manner that would make those observations useful and deserving of patent

protection. *Le Roy v. Tatham*, 63 U.S. (22 How.) 132, 137 (1859). As a result, "manifestations of laws of nature" are "free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130. Natural phenomena and abstract ideas represent "the basic tools of scientific and technological work," *Benson*, 409 U.S. at 67, that should remain "part of the storehouse of knowledge," *Funk Bros.*, 333 U.S. at 130, ineligible for patenting.

On this basis, the Court has reasoned that "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter" under Section 101, *Chakrabarty*, 447 U.S. at 309, nor can a patent issue claiming the qualities of natural products like metals or bacteria. *Funk Bros.*, 333 U.S. at 130. "Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity." *Chakrabarty*, 447 U.S. at 309.

But the Court and the Federal Circuit have also recognized that categories of unpatentable abstract natural principles at times may be difficult to define, particularly so for processes. Indeed, no clear definition of "abstract" has emerged. *Flook*, 437 U.S. at 589 ("The line between a patentable 'process' and an unpatentable 'principle' is not always clear."); *Bilski*, 130 S.Ct. at 3236 (noting the absence of a "satisfying account of what constitutes an unpatentable abstract idea") (Stevens, J., concurring); *see also Research Corp. Tech., Inc. v. Microsoft Corp.*, 627 F.3d 859, 868 (Fed. Cir. 2010)

("[T]his court also will not presume to define 'abstract' beyond the recognition that this disqualifying characteristic should exhibit itself so manifestly as to override the broad statutory categories of eligible subject matter and the statutory context that directs primary attention on the patentability criteria of the rest of the Patent Act.").

1. Is the Claimed Process Directed to an Application of an Abstract Natural Principle?

Although a patent claim directed to an abstract natural principle is not patent-eligible, the Court has long recognized that "[i]t is now commonplace that an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection." *Diehr*, 450 U.S. at 187-88 (emphasis in original) (citation omitted); *see Mackay Radio & Tel. Co. v. Radio of America*, 306 U.S. 86, 94 (1939) ("While a scientific truth, or the mathematical expression of it, is not a patentable invention, a novel and useful structure created with the knowledge of scientific truth may be."); *Le Roy*, 63 U.S. at 137 ("There can be no patent for a principle; but for a principle so far embodied and connected with corporeal substances as to be in a condition to act and to produce effects in any trade, mystery, or manual occupation, *there may be a patent*"). (emphasis added). A "claim drawn to subject matter otherwise statutory does not become non-statutory simply because it uses a mathematical

formula" or other principle of the natural world. *Diehr*, 450 U.S. at 187.

The concept of an "application of a law of nature" is similar to the transformation of an abstract idea. It is the application of a law of nature that converts an observation made in the natural world into a process having a "new and useful end," which is required for patent-eligible subject matter. *See Benson*, 409 U.S. at 67 (quoting *Funk Bros.*, 333 U.S. at 130). For claims reciting "a mathematical formula (or scientific principle or phenomenon of nature)," the primary inquiry is to determine "whether the claim is seeking patent protection for that formula in the abstract." *Diehr*, 450 U.S. at 191. The relevant distinction for this threshold analysis is between "products of nature . . . and human-made inventions." *J.E.M. Ag Supply*, 534 U.S. at 130 (quoting *Chakrabarty*, 447 U.S. at 313).

Diehr set forth three cardinal rules that must be followed when assessing whether a claimed process crosses the threshold from a patent-ineligible, abstract natural principle to the concrete human-made realm of patent-eligible subject matter.

1. The claim "must be considered as a whole." *Diehr*, 450 U.S. at 188; *see Bilski*, 130 S.Ct. at 3230; *Flook*, 437 U.S. at 590 ("a process is not unpatentable because it contains a law of nature or a mathematical algorithm").

2. "It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Diehr*, 450 U.S. at 188; *Bilski*, 130 S.Ct. at 3230.

3. "The 'novelty' of any element or steps in a process, or even of the process itself, is of no relevance in determining whether the subject matter of a claim falls within the § 101 categories of possibly patentable subject matter." *Diehr*, 450 U.S. at 188-89; *see id.* at 193 n.15 ("The fact that one or more of the steps in respondents' process may not, in isolation, be novel or independently eligible for patent protection is irrelevant to the question of whether the claims as a whole recite subject matter *eligible* for patent protection under § 101.") (emphasis in original).

Considering the claim as a whole respects the overall patentability framework, as claims "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention." 35 U.S.C. 112, ¶ 2. For processes, an inventor's characterization of the invention is critical because "a new combination of steps in a process may be patentable even though all the constituents in the combination were well known and in common use before the combination was made." *Diehr*, 450 U.S. at 188.

But determining whether a claimed process is directed to a law of nature or a natural phenomenon or an application of a natural law or natural phenomenon can be as difficult as determining whether an invention claims an abstract principle.

NYIPLA respectfully submits that the machine-or-transformation test is a useful tool for this analysis and, if satisfied, creates a safe harbor of patent-eligible subject matter, namely patentable applications of laws of nature and patentable applications of natural phenomena.

2. Claimed Processes that Satisfy the Machine-or-Transformation Test Are Patent-Eligible

For processes that appear to cover a fundamental principle, *Diehr* noted that "[t]ransformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Diehr*, 450 U.S. at 184 (quoting *Benson*, 409 U.S. at 70) (internal quotations omitted); *see also Flook*, 437 U.S. at 588 n.9 ("An argument can be made, however, that this Court has only recognized a process as within the statutory definition when it either was tied to a particular apparatus or operated to change materials to a 'different state or thing.'") (citing *Cochrane v. Deener*, 94 U.S. 780, 787-88 (1876)). The Court has confirmed that the machine-or-transformation test remains "a useful and important clue, an

investigative tool, for determining whether some claimed inventions are processes under § 101." *Bilski*, 130 S.Ct. at 3227.

This appeal presents the Court with the perfect opportunity to confirm the vitality of the machine-or-transformation test in the context of the general principles governing patent eligibility. But NYIPLA respectfully submits that the machine-or-transformation test is a useful tool only if an explicit safe harbor exists for claimed processes that meet its requirements.

A transformation, if present, provides a compelling indication that the claimed inventive process is neither abstract nor directed to a natural phenomenon. *Chakrabarty*, 447 U.S. at 310 ("Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101."); *Flook*, 437 U.S. at 594 ("Even though a phenomenon of nature or mathematical formula may be well known, an inventive application of the principle may be patented. Conversely, discovery of such a phenomenon cannot support a patent unless there is some other inventive concept in its application.").

The mere fact that a patentee is able to articulate a transformative step in a claim "connected with corporeal substances as to be in a

condition to act and to produce effects in any trade, mystery, or manual occupation" demonstrates that the claim is not to a principle, but is directed to an application of a law of nature rather than the natural phenomenon itself for which "there may be a patent". *Le Roy*, 63 U.S. at 138.

Consistent with the broad scope of Section 101, the *type* of the transformation present in a process is immaterial to determining patent eligibility, because *any* transformation will carry a claimed invention across the § 101 threshold. *Tilghman v. Proctor*, 102 U.S. 707, 728 (1881) (discussing that a process may provide the "means" to achieve a "useful result," even though "[a] process is an act, or a mode of acting . . . [that is] a conception of the mind, seen only by its effects when being executed or performed."). While other analyses may similarly define the presence of an application of a fundamental principle, NYIPLA respectfully submits that once the machine-or-transformation test is met, the subject-matter eligibility requirement of Section 101 is likewise met. This is not to say that the machine-or-transformation test is the exclusive framework for determining what is patentable subject matter under Section 101—it is not. *Cf. Bilski*, 130 S.Ct. at 3227.

Since the Court's pronouncements in *Bilski*, the Federal Circuit has recognized that Section 101 is a "coarse eligibility filter, not the final arbiter of patentability." *Classen Immunotherapies, Inc. v. Biogen IDEC*, ___ F.3d ___, No. 2006-1634, -1649,

2011 U.S. App. LEXIS 18126 at *22 (Fed. Cir. Aug. 31, 2011) (internal quotation omitted); *see also Research Corp.*, 627 F.3d at 868 (noting that Section 101 "directs primary attention to 'the conditions and requirements of [Title 35]'") (quoting 35 U.S.C. § 101).

Though not exclusive, if a court finds sufficient facts to satisfy the requirements of the machine-or-transformation test, and those findings are correct, then further attack on the subject matter eligibility of the claimed invention should end. All remaining questions of patentability can and should be resolved as separate analyses under 35 U.S.C. §§ 102, 103 and 112. *See Bilski*, 130 S.Ct. at 3225; *id.* at 3238 (Stevens, J. concurring) (noting the "risk of merely confirming our preconceived notions of what should be patentable or of seeing common attributes that track the familiar issues of novelty and obviousness that arise under other sections of the statute but are not relevant to § 101") (internal quotation and citation omitted).

Over a century ago, the Court considered whether a method directed to expanding sheet metal by simultaneously cutting and stretching it was eligible for patent protection, given that, at the time, process patents only related to chemical reactions and elemental changes. *Expanded Metal Co. v. Bradford*, 214 U.S. 366, 374-75, 382 (1909) (noting the parties' disagreement over whether *Corning v. Burden*, 56 U.S. (15 How.) 252 (1854) and *Risdon Locomotive Works v. Medart*, 158 U.S. 68 (1895) held

that patentable processes did not "include methods or means which are affected by mere mechanical combinations"). Noting that *Cochrane v. Deener*, 94 U.S. 780, had previously "sustained a process patent involving mechanical operations," the Court concluded that patent-eligible processes were not limited to chemical action or elemental changes:

> A process is a mode of treatment of certain materials to produce a given result. It is an act, or a series of acts, performed upon the subject matter to be transformed and reduced to a different state or thing. If new and useful, it is just as patentable as is a piece of machinery. In the language of the patent law, it is an art. The machinery pointed out as suitable to perform the process may or may not be new or patentable; whilst the process itself may be altogether new, and produce an entirely new result. *The process requires that certain things should be done with certain substances, and in a certain order; but the tools to be used in doing this may be of secondary consequence.*

Bradford, 214 U.S. at 384 (quoting *Cochrane*, 94 U.S. at 787) (emphasis added). Today, the Court should continue resisting calls to limit the scope of those transformative steps that can render a claimed process patent-eligible.

Taken as a whole, the useful clue provided by the transformation prong of the machine-or-transformation test illuminates those ways in which an invention provides something more than mere observations, concepts and ideas that exist in nature—subject matter that is not itself directly patentable.

C. Practical Applications of Laws of Nature Are Patent-Eligible

Here, the parties to this appeal ask the Court to decide whether the claimed correlations are patent ineligible like the relationship between variables defined by a mathematical algorithm or formula. In that regard, the parties dispute whether the claimed processes "wholly preempt" all uses of natural correlations between certain metabolite levels in the body and patient health, which the parties presume to be a law of nature. Pet.21 (quoting *Benson*, 409 U.S. at 71-72); Br.Opp. 26-27; *see also* Pet.15.

The Court should clarify that its precedents do not provide for a "preemption" analysis as a stand-alone patent-eligibility test, however. The key question established in the *Diehr* framework is whether a claimed invention is directed to one of the

three fundamental principles or only an application of those fundamental principles. Because all patent claims preempt the practice of an invention, to perform any useful work concerning patent eligibility under Section 101, a consideration of preemption *must* incorporate a critical assessment of whether the claim at issue actually claims a fundamental principle as a fundamental principle in contrast to an application of that principle. Otherwise, concluding that a claim "preempts" others from practicing a particular process does nothing but identify a broad claim that may, in fact, be unpatentable for failing to meet other conditions of patentability, but nevertheless is patent-eligible under Section 101.

Instead, courts must begin with and look to the long-established two-part framework governing patent eligibility under Section 101: (1) Does the claimed subject matter fall within one of the four statutory classes of patent-eligible subject matter? (2) Is the claimed subject matter directed to a law of nature, a physical phenomenon or an abstract idea?

Determining whether the general subject matter of an invention is a law of nature or a physical phenomenon should be a relatively straightforward threshold inquiry. Some members of the Court, however, have noted that the actual scope of non-patent-eligible laws of nature remains elusive. *See Lab. Corp. of America Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 134 (2006) (Breyer, J., dissenting) (stating that "the category of nonpatentable '[p]henomena of nature,' like the

categories of 'mental processes' and 'abstract intellectual concepts,' is not easy to define").

In *Benson*, the Court considered the patentability of a mathematical algorithm, defined as a "procedure for solving a given type of problem." 409 U.S. at 65. The *Benson* court went on to equate mathematical algorithms to "phenomena of nature," 409 U.S. at 67, a classification later confirmed in *Flook*, which held that mathematical algorithms are unpatentable subject matter regardless of their novelty or utility. *Flook*, 437 U.S. at 585. One member of the Court later recognized, however, that "the inclusion of the ambiguous concept of an 'algorithm' within the 'law of nature' category of unpatentable subject matter has given rise to the concern that almost any process might be so described and therefore held unpatentable." *Diehr*, 450 U.S. at 219 (Stevens, J., dissenting).

Like mathematical algorithms and formulas, correlations between variables may establish useful relationships between measurable features of the natural world. Assuming *arguendo* that the claimed correlations in this case are directed to laws of nature, if the claimed processes cover only practical applications of those laws of nature, they are "at the very least not barred at the threshold by § 101." *Diehr*, 450 U.S. at 188. Under the general principles reaffirmed in *Bilksi*, *supra*, § I, the Court may also rely on the machine-or-transformation test as a useful clue: if the claimed processes include one or more transformative steps, the claimed invention is

sufficiently non-abstract and non-natural to be patent-eligible.

Regardless of the conclusion reached by this analysis, the Court should resist invitations to exclude certain methods from the broad scope of patentable subject matter. Because technology may evolve faster than descriptive categories may be defined, Section 101 must remain a "dynamic provision designed to encompass new and unforeseen inventions." *J.E.M. Ag Supply*, 534 U.S. at 135. Given the several competing public policy interests at play, the Court has observed that only Congress may endeavor to create such a limitation. *See Bilski*, 130 S.Ct. at 3227 ("A categorical rule denying patent protection for 'inventions in areas not contemplated by Congress . . . would frustrate the purposes of the patent law.'") (quoting *Chakrabarty*, 447 U.S. at 315).

Writing separately to express additional views about the "rising number of challenges" to patent eligibility, in which "litigants continue to urge this court to impose limitations not present in the statute," Chief Judge Rader recently stated that

> [s]ubject matter eligibility under section 101 has become the 'substantive due process' of patent law—except that reading non-procedural requirements into the constitutional word 'process' has more historical and

> contextual support than reading abstractness into the statutory word 'process' because Title 35 already contains ample protections against vague claims. *See* 35 U.S.C. § 112. Indeed it is difficult to 'invent' any category of subject matter that does not fit within the four classes acknowledged by Title 35: process, machine, [article of] manufacture, or composition of matter. This court should decline to accept invitations to restrict subject matter eligibility.

Classen, *supra*, 2011 U.S. App. LEXIS 18126, at *45 (Rader, C.J., concurring). Chief Judge Rader went on to explain that

> patentability, as opposed to subject matter eligibility, depends on the *substantive* conditions in the rest of the title. *See* 35 U.S.C. §§ 102, 103, 112. Many litigation-spawned applications of section 101 do not focus on categories of subject matter that deserve no patent protection but on the particularities of claim language, a question of

> patentability depending on prior art and adequate disclosure.

Id. at *51 (Rader, C.J., concurring).

NYIPLA concurs wholeheartedly with Chief Judge Rader's views, and urges the Court, by reaffirming the clear rules it has already established for patent eligibility under Section 101, to put an end to the extra-statutory efforts of the lower courts to improperly restrict the broad scope of patentable subject matter.

Given the past pronouncements of this Court and the silence of Congress on this issue, there is no basis for excluding processes directed to analyzing the chemicals in a patient's body from patent eligibility given the broad scope of § 101. Even if those biologically-relevant chemicals themselves are naturally-existing products, their *application* in a useful and concrete process would be, and should be patent-eligible under *Diehr* and *Bilksi*. And under the Court's general framework, this patent eligibility exists even though a claim may fail to meet other conditions of patentability, either justifying the claim's rejection during prosecution or rendering an issued claim invalid. *See Bilski*, 130 S.Ct. at 3225.

II. PATENTS ARE AN IMPORTANT AND VALUABLE PART OF OUR ECONOMY AND PROMOTE THE PROGRESS OF THE USEFUL ARTS

Patents play an important role in promoting the "progress" of the "useful Arts" and stimulating innovation. U.S. Const. art. 1, § 8, cl.8. The patent system promotes that progress in a variety of ways.

As this Court recognized, one way of promoting progress is by rewarding innovation with patent rights. *See, e.g.*, *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 730-31 (2002) ("The patent laws 'promote the Progress of Science and useful Arts' by rewarding innovation with a temporary monopoly.") (quoting U.S. Const. art. I, § 8, cl. 8)); *Chakraharty*, 447 U.S. at 307 (explaining that "[t]he Constitution grants Congress broad power to legislate to 'promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.' Art. I, § 8, cl. 8" and that "[t]he patent laws promote this progress by offering inventors exclusive rights for a limited period as an incentive for their inventiveness and research efforts") (citations omitted).

President Lincoln, describing the development of a patent system as an important event "greatly favoring and facilitating useful discoveries and inventions," explained:

> Next came the patent laws. These began in England in 1624, and in this country with the adoption of our Constitution. Before then any man [*might*] instantly use what another man had invented, so that the inventor had no special advantage from his invention. The patent system changed this, secured to the inventor for a limited time exclusive use of his inventions, and thereby added the fuel of interest to the fire of genius in the discovery and production of new and useful things.

Abraham Lincoln, *Lecture on "Discoveries, Inventions and Improvements,"* delivered before the Library Association of Springfield, Illinois, Feb. 22, 1860, *reprinted in* THE WISDOM OF ABRAHAM LINCOLN 104 (Marion Mills Miller ed. 1908).[3]

But this is not the only way patent systems "promote progress." Public disclosure in patents is also important to innovative progress. Shortly after

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[3] Besides being the sixteenth president of the United States, Mr. Lincoln was the inventor on U.S. Patent No. 6,469, entitled "Buoying Vessels Over Shoals," (filed Mar. 10, 1849).

Congress passed the 1952 amendments to the Patent Act, Judge Rich—its principal architect—presented a series of lectures on the then-new Act, providing useful insight into the varying purposes of patent laws. Discussing how the patent laws serve "incremental inventions" and "become part of the technical literature," Judge Rich stated:

> In the remote corners of the most crowded arts, progress is made by the proliferation of ideas, different and unobvious ways of doing the same thing, so that the reservoir of inventions fills up. It should never be forgotten that patented inventions are published and become a part of the technical literature. This publication itself promotes progress in the useful arts and it is the prospect of patent rights which induces the disclosure and the issuance of the patent which makes it available.

Giles S. Rich, *The Principles of Patentability*, 42 J. Pat. Off. Soc'y 75, 83 (1960) (emphasis added).

Those wise words from almost half a century ago ring particularly true when it comes to new and unforeseen inventions in our modern age. Today's inventions—aided by yesterday's technological

advances—appear at a bewildering pace, casting doubt on the utility of any rigid categorization of patent-eligible subject matter, however carefully crafted or well-intentioned. Patent laws must remain flexible enough to welcome future developments, not squelch them. *See Bilski,* 130 S.Ct. at 3227; *Benson*, 409 U.S. at 71 (stating that the Court's "purpose" is not to "freeze process patents to old technologies, leaving no room for the revelations of the new onrushing technology").

Our patent system has permitted Judge Rich's "reservoir of [disclosed] inventions" to foster ingenuity, create new technologies, and build entire industries for over two hundred years. That progress must continue and encourage the advances of tomorrow.

CONCLUSION

The Court should reaffirm the well-established governing principles for determining whether, as a threshold issue, a claimed process is patent-eligible under 35 U.S.C. § 101, and reject the use of any extra-statutory test or theory as a substitute for this settled law.

Respectfully submitted,

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-1150

In The
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(d/b/a MAYO MEDICAL LABORATORIES)
and MAYO CLINIC ROCHESTER,

Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,

Respondent.

**On Writ Of Certiorari To The
United States Court Of Appeals
For The Federal Circuit**

BRIEF OF NINE LAW PROFESSORS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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INTERESTS OF *AMICI CURIAE*

This brief is filed on behalf of the undersigned Law Professors identified in Appendix A.[1]

Law Professors teach and write about patents, intellectual property, and constitutional law. Law Professors are concerned that the Patent Act should be construed in this case consistently with: (1) the historic and constitutional requirement to treat as prior art discoveries of laws of nature, physical phenomena, and abstract ideas, and the consequent exclusion from patent eligibility of claimed applications of such discoveries that lack any inventive creativity; (2) legislative recognition and preservation of these historic requirements in Section 101 of the Patent Act; and (3) the benefits of excluding at the threshold under Section 101 claims to uncreative applications of such discoveries. By protecting the public domain of science, nature, and ideas from encroachment by such claims, the Court will continue to promote scientific and technological development for human benefit. Failure to require such prior art treatment and inventive creativity in applications would threaten continued scientific and technological, progress. *Amici* urge the Court to avoid this result.

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[1] Letters of the Parties' consent to file amicus briefs are on file with the Court. This brief was not authored in whole or in part by counsel for any party. No one other than *Amici* and their counsel made a monetary contribution to preparing or submitting this brief.

SUMMARY OF THE ARGUMENT

In *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), this Court reiterated the requirement to treat as prior art new but ineligible discoveries of laws of nature, physical phenomena, and abstract ideas. The very concept of invention thus requires a creative advance *in the application* of any such discovery. For over two centuries, prior art treatment of ineligible discoveries and the requirement for additional creativity have protected the public domain from encroachment by private patent rights. Given prior art treatment, additional creativity ("invention") – like originality in copyright law – is a constitutional requirement, as recognized in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Patents on uncreative applications of ineligible discoveries would effectively withdraw the knowledge contained in those discoveries from the public domain. Prior art treatment derives from a historic moral duty for scientists to freely share such discoveries, which informs the constitutional meaning of "Inventors" for *their* "Discoveries." This Court should expressly recognize prior art treatment and the requirement for creativity in the application as Constitutional requirements.

Consistent with the Constitution, the Patent Act since 1790 has been construed to require that there be creativity in the application of any scientific, natural, or abstract discovery in order for a patent-eligible "invention" to exist. This requirement and the

prior art treatment of new discoveries were preserved in the 1952 Patent Act, by codifying in both Sections 101 and 103 the judicial requirement for "invention" that had been developed under the predecessor to Section 101. Neither Section 100(b)'s "new use" authority nor Section 103's "non-obviousness" terminology altered the requirement for invention, and thus prior art treatment and creativity in the application of ineligible discoveries remain requirements for eligibility under Section 101. Eliminating such requirements from the statute would raise serious constitutional questions.

Without prior art treatment and the requirement for creativity in the application of excluded discoveries, the claims at issue might improperly survive scrutiny under Sections 101 (eligibility), 102 (novelty), 103 (non-obviousness), and 112 (adequacy of disclosure). Given preservation of prior art treatment and the creativity requirement, threshold eligibility decisions under Section 101 perform an efficient gate-keeping role. Uncreative applications of ineligible discoveries like those at issue here will be both ineligible under Section 101 and necessarily unpatentable under Section 103. Obviousness decisions require prior art searching and complex factual evaluations that should not normally be required for such eligibility decisions. Excluding such claims under Section 101, moreover, sends important signals about protecting the public domain from encroachment and the need for public

funding of discoveries, and directs investment and activity towards creative and patentable applications of ineligible discoveries.

ARGUMENT

I. The Court Should Reaffirm that Ineligible Discoveries Must Be Treated as Prior Art and that Invention Requires Creativity in Their Application.

In *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), the Court reiterated that new discoveries of "'laws of nature, physical phenomena, and abstract ideas'" (i.e., scientific principles, natural phenomena and products, and fundamental information; science, nature, and ideas for short) are not patent-eligible inventions. *Id.* at 3225 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980)). The "concepts" covered by these "exceptions"[2] to the broad legislative definition of an eligible invention in Section 101 of the Patent Act "are 'part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none.'" *Id.* (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)).

[2] *But see In re Alappat*, 33 F.3d 1526, 1553 n.13 (Fed. Cir. 1994) (en banc) (Archer, C.J., dissenting) (noting the error of characterizing "nonstatutory subject matter . . . as an "'exception' to § 101. Defining patentable subject matter is the *raison d'être* of § 101.") (citation omitted).

In other words, such pre-existing or fundamental information and things are and should remain part of the public domain, free from exclusive private property rights.

Of equal importance, the Court in *Bilski* reiterated its precedents that such categorically excluded discoveries must be treated as already known prior art, even if they were not in fact known or disclosed before their discovery by the applicant:

> The Court concluded [in *Parker v. Flook*] that the process at issue there was "unpatentable under § 101, not because it contain[ed] a mathematical algorithm as one component, but because once that algorithm [wa]s *assumed to be within the prior art*, the application, considered as a whole, contain[ed] no patentable invention." . . . As the Court later explained, *Flook* stands for the proposition that the prohibition against patenting abstract ideas "cannot be circumvented by attempting to limit the use of the formula to a particular technological environment" or adding "insignificant postsolution activity."

Id. at 3230 (quoting *Parker v. Flook*, 437 U.S. 584, 594 (1978), and *Diamond v. Diehr*, 450 U.S. 175, 191-92 (1981)) (emphasis added); *see Flook*, 437 U.S. at 595 ("If we assume that that method was also known, as we must under the reasoning in *Morse*") (citing *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 115 (1854)).

As a result of its prior art treatment, "the discovery of such a[n ineligible] phenomenon cannot support a patent unless there is some other *inventive*

concept in its application." *Flook*, 347 U.S. at 594 (emphasis added). In other words, a patent-eligible "invention" must reflect *inventive* creativity that is additional to any *scientific* creativity involved in making the discovery and to mere application of the discovered knowledge or thing to a particular context or a specific use. The requisite *inventive* creativity cannot be supplied by adding conventional or otherwise insignificant elements or limitations to patent claims. Such additions reflect the creativity only of a "competent [legal] draftsman," not of an inventor. *Id.* at 590; *see Diehr*, 450 U.S. at 192 ("To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible. . . ."); *cf. Alappat*, 33 F.3d at 1554 (Archer, C.J., dissenting) ("The discovery of music does not become patentable subject matter simply because there is an arbitrary claim to some structure."). As this Court previously stated in *Flook*:

> The question . . . is whether the identification of a limited category of useful, though conventional, post-solution applications of such a formula makes respondent's method eligible for patent protection. . . . The notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process exalts form over substance.

Flook, 437 U.S. at 585, 590.

These historic requirements for prior art treatment and for *inventive* creativity *in the application* of

ineligible discoveries protect the public domain of science, nature, and ideas from piecemeal encroachment by patent claims. Claims drawn to uncreative but specific applications of a categorically ineligible discovery may have a more limited scope than claims to the discovery itself. Consequently, such claims may not "'wholly pre-empt'" all applications of an ineligible discovery. *Bilski*, 130 S. Ct. at 3230 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 72 (1972)). But they will add nothing to the public's entitlement to benefit and to create inventions from the discovery. Without prior art treatment and the requirement for creativity in the application, large swaths of the public domain that should remain free for public use and creative investigation could be subjected to a plethora of patent rights.

The Court in this case should reaffirm that the Patent Act requires prior art treatment of ineligible discoveries and creativity in the application of such discoveries. These requirements generate and protect the public domain of science, nature, and ideas. Such prior art treatment "has made all the difference." Robert Frost, *The Road Not Taken,* in Six American Poets 208 (Joel Conarroe ed. Vintage Books 1991) (1920). The Court also should affirm here that these historic requirements are mandated by the Constitution, as reflected in the language "Inventors to their respective . . . Discoveries." Art. I, § 8, cl. 8; *see, e.g.*, *Kewanee Oil Co. v. Bicron Corp.*, 416 U.S. 470, 476 (1974) ("discovery is something less than invention"); Anthony W. Deller, *The United States patent system*,

in Mainly on patents: The use of industrial property and its literature 50-52 (Felix Liebesny ed., 1972) (distinguishing "'mere discovery'" from "invention") (quoting *Morton v. New York Eye Infirmary*, 17 F. Cas. 879, 882 (C.C.S.D.N.Y. 1862) (No. 9,865)).

A. Prior Art Treatment of Excluded Discoveries and Creativity in Their Application Are Long-Standing Requirements of the Patent Act.

The requirement for prior art treatment of new discoveries found its first *explicit* statement in American patent law in 1854 in *O'Reilly*, relying on the English precedent of *Nielson v. Harford*, 151 Eng. Rep. 1266 (1841):

> Neilson claimed no particular mode of constructing the receptacle, or of heating it. . . . [T]he court at first doubted, whether it was a patent for any thing more than the discovery that hot air would promote the ignition of fuel better than cold. And if this had been the construction, the court, it appears, would have held his patent to be void; *because the discovery of a principle in natural philosophy or physical science, is not patentable.*
>
> But after much consideration, *it was finally decided that this principle must be regarded as well known,* and that *the plaintiff had invented a mechanical mode of applying it to furnaces*; and that his invention consisted in interposing a heated receptacle, between the blower and the furnace, and by this means

> heating the air after it left the blower, and before it was thrown into the fire. . . .
>
> Undoubtedly, the principle that hot air will promote the ignition of fuel better than cold, was embodied in this machine. *But the patent was not supported because this principle was embodied in it.* . . .
>
> . . . If the Court of Exchequer had said that Neilson's patent was for the discovery, that hot air would promote ignition better than cold, and that he had an exclusive right to use it for that purpose, there might, perhaps, have been some reason to rely upon it. But the court emphatically denied this right to such a patent.

O'Reilly, 56 U.S. (15 How.) at 115-16 (emphasis added). One year earlier, the Court had explicitly stated that scientific, natural, and abstract discoveries are ineligible for patent protection. *See Le Roy v. Tatham*, 55 U.S. (14 How.) 156, 175 (1853) ("[a] principle, in the abstract, is a fundamental truth; an original cause; a motive; these cannot be patented, as no one can claim in either of them an exclusive right."). But these requirements had a long history, predating the Constitution.

Before and through the late 18th century, "invention" had a technical meaning that distinguished it from discoveries of scientific principles, natural phenomena, and fundamental information (as well as

from discoveries of exploration or in the liberal and fine arts).[3] Discoveries of science, nature, and ideas, and the world they described, were thought to originate from God. Accordingly, such discoveries were not thought to be human creations that were the proper objects of exclusive property rights.[4]

Further, scientists who made such discoveries were thought to owe moral duties to share their discoveries freely with the public, which was then entitled to benefit from the information. As Lord

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[3] *See, e.g.*, Edward C. Walterscheid, The Nature of the Intellectual Property Clause: A Study in Historical Perspective 365-66, 375-76 (William S. Hein & Co. 2002) hereinafter "Walterscheid, *Study*") (arguing that "Discoveries" of "Inventors" are limited to the "useful arts," which excludes "anything not made or created by man"); John R. Thomas, *The Patenting of the Liberal Professions*, 40 B.C. L. Rev. 1139, 1164-65 (1999).

[4] *See* Christine MacLeod, Inventing the Industrial Revolution: The English Patent System 1660-1800, at 198-203 (Cambridge Univ. Press 2002) (1988); *cf. Feist Publ'ns, Inc. v. Rural Tele. Serv. Co.*, 499 U.S. 340, 341 (1991) (distinguishing "discovery" from "creation" in the copyright context; holding that facts cannot be original creations of their discoverers); 1 William C. Robinson, The Law of Patents for Useful Inventions 93-94 (Little, Brown 1890) (surveying earlier efforts to define invention); Letter from Thomas Jefferson to Isaac MacPherson (Aug. 13, 1813), in Thomas Jefferson, the Portable Thomas Jefferson 529-30 (Merrill D. Peterson ed., Penguin Books 1977) (1975) (hereinafter "Jefferson Letter") (explaining why ideas are not naturally subject to property rights); *see generally* Walterscheid, *Study*, *supra*, at 39 (explaining how the medieval belief that creativity came from God delayed the development of intellectual property, as it was thought improper to seek commercial benefit from what had been given freely by God).

Camden stated in 1774, scientists are "intrusted by Providence with the delegated power of imparting to their fellow-creatures that instruction which heaven meant for universal benefit; they must not be niggards to the world, or hoard up for themselves the common stock." 17 The Parliamentary History of England col. 999 (William Cobbett ed., 1806-20) (1774); *see* 1 Robinson, *supra*, at 39 ("To benefit by the discoveries of his fellow-men is thus not only a natural right, it is also the natural duty which every man owes to himself and to society; and the mutual, universal progress thence resulting is the fulfillment of the earthly destiny of the human race.").

It is this moral duty of scientists to create, protect, and disseminate a public domain of science, nature, and fundamental information[5] that grounds prior art treatment of ineligible discoveries in patent law. The moral duty is effectuated by treating a new (*i.e.*, not previously disclosed) discovery as prior art, constructively giving it to the public when a patent application discloses it. This moral duty is distinctive by *creating* a public domain of science, nature, and ideas, although it overlaps with utilitarian beliefs in the social benefits of *protecting* and *disseminating* the public domain that exists as a result of non-patent disclosures. *See* 1 Robinson, *supra*, at 39; *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S.

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[5] *See generally* Robert K. Merton, *The Normative Structure of Science*, in Robert K. Merton The Sociology of Science 275-77 (1973).

124, 128 (2006) (Breyer, J., dissenting from dismissal as improvidently granted) ("protection in such cases, despite its potentially positive incentive effects, would too often severely interfere with, or discourage, development and the further spread of useful knowledge itself"); *cf.* Michael J. Madison, Brett M. Frischmann & Katherine J. Strandburg, *Constructing Commons in the Cultural Environment*, 95 Cornell L. Rev. 657, 659-65 (2010) (discussing created institutions that treat knowledge as a commons).

Shortly after the Constitution was enacted, English and American courts explicitly declared the implicit, widespread understanding that patents could not issue for scientific discoveries or abstract ideas. *See, e.g.*, *Boulton v. Bull*, 126 Eng. Rep. 651, 667 (1795) (Lord Eyre, C.J.) (no patents for "mere principle[s]"); *id.* at 663 (Buller, J.) (no patents for "an idea or principle alone"); *Lowell v. Lewis*, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8,568) ("It has been often decided, that a patent cannot be legally obtained for a mere philosophical[6] or abstract theory."). The Court recognized by the middle of the 19th century that prior art treatment was logically entailed by the exclusion of such discoveries and of their underlying scientific creativity from the patent system. As the Court explained in *O'Reilly*, Neilson's right to a patent could not have been premised either

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[6] "Philosophical" was then understood to mean pertaining to the natural sciences. *See, e.g.*, The Compact Edition of the Oxford English Dictionary 180 (Oxford Univ. Press 1971).

on the discovery itself or on the fact that the discovery was applied in and through a machine. *See* 56 U.S. (15 How.) at 115-16. Rather, Neilson's patent could be justified, if at all, only by some different, inventive creativity. *See id.*

Allowing patents for uncreative applications would *effectively* provide exclusive rights in and impermissibly reward the ineligible discovery itself.[7] Allowing such patents would constrict the public domain by restricting the use of such discoveries.[8] As aptly stated by the Ninth Circuit near the end of the 19th century:

> [E]mployment of [a scientific discovery] in the modes or through the instrumentalities by which it is applied in nature is a mere limitation of what every man is able to perceive and reproduce as well as [t]he [patentee]. All endeavors to confine it to himself are at once futile and *unjust*. . . . Not until some new instrument or method is contrived for its

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[7] *See, e.g.*, Hector M. Holmes, *Patent Rights for Scientific Discoveries by C.J. Hamson*, 45 Harv. L. Rev. 1431, 1432 (1932) ("a scientific discoverer is not a creator").

[8] Similar concerns animate the copyright doctrine of merger, which precludes protection for an author's expression if it "would effectively accord protection to the idea itself." *Kregos v. Associated Press*, 937 F.2d 700, 705 (2d Cir. 1991). This is because "ideas are too important to the advancement of knowledge to permit them to be under private ownership." *CCC Info. Servs., Inc. v. Maclean Hunter Market Repts., Inc.*, 44 F.3d 61, 69 (2d Cir. 1994); *see Baker v. Selden*, 101 U.S. 99, 103 (1879).

> direction *towards ends which it cannot naturally accomplish* does his creative genius manifest itself.

Wall v. Leck, 66 F. 552, 558 (9th Cir. 1895) (citing 1 Robinson, *supra*, § 136) (emphasis added).

Unless the patent claimed a creative use or thing that was not analogous to the discovery itself, there could be no patent-eligible invention. *See Ansonia Brass & Copper Co. v. Electric Supply Co.*, 144 U.S. 11, 18 (1892) ("nothing is better settled in this court than that the application of an old process to a new and analogous purpose *does not involve invention*, even if the new result *had not before been contemplated*.") (emphasis added); *Howe v. Abbott*, 12 F. Cas. 656, 658 (C.C.D. Mass. 1842) (No. 6,766) ("The application of an old process to manufacture an article, to which it had never before been applied, is not a patentable invention."); *cf. Hotchkiss v. Greenwood*, 52 U.S. (11 How.) 248, 267 (1851) ("[T]here was an absence of that degree of skill and ingenuity which constitute essential elements of every *invention*. . . . [T]he improvement is the work of the skilful mechanic, not that of the inventor.") (emphasis added). Novelty and utility have never been sufficient for patent eligibility. Were it otherwise, two centuries of this Court's eligibility precedents would have come out differently.

Two decades after *O'Reilly*, this Court relaxed somewhat the way that patent-eligible inventive creativity could be *claimed*, permitting patents for methods that *creatively* applied discoveries but were

not restricted to particular arrangements of specific machines. *See Cochrane v. Deener*, 94 U.S. 780, 787-88 (1876). But this Court has continued to require creativity in the application itself.[9] Claiming uncreative but limited applications of discoveries remains insufficient,[10] even if specific machines are employed

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[9] *See, e.g., Dolbear v. American Bell Telephone Co.*, 126 U.S. 1, 534 (1888) ("In the present case the claim is not for the use of a current of electricity in its natural state as it comes from the battery, but for putting a continuous current, in a closed circuit, into a certain specified condition, suited to the transmission of vocal and other sounds, and using it in that condition for that purpose"); *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939) ("We assume, without deciding the point, that this advance was *invention* even though it was achieved by the logical application of a known scientific law to a familiar type of antenna.") (emphasis added); *Funk Bros. Seed Co.*, 333 U.S. at 131 ("The aggregation of select strains of the several species into one product is an application of that newly-discovered natural principle. But however ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants."). *See generally* Joshua D. Sarnoff, *Patent Eligible Inventions after* Bilski: *History and Theory*, 63 Hastings L.J. __ (forthcoming, Feb. 7, 2011 draft at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1757272) (tracing this history with additional examples).

[10] *See, e.g., Bilski*, 130 S. Ct. at 3231 ("*Flook* established that limiting an abstract idea to one field of use or adding token postsolution components did not make the concept patentable."); *Chakrabarty*, 440 U.S. at 310 (new biological things must have "markedly different characteristics" from natural discoveries); *id.* (invention requires "a product of human ingenuity 'having a distinctive name, character [and] use.'") (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)); *American Fruit Growers, Inc. v. Brogdex* Co., 283 U.S. 1, 13 (1931) ("a new and different article must emerge").

or physical transformations are achieved.[11] *See* Brief of Eleven Law Professors and AARP as *Amici Curiae* in Support of Respondent, at 17-22, *Bilski v. Kappos*, 130 S. Ct. 3218 (2010) (No. 08-964).

B. These Historic Requirements Should Be Recognized as Constitutional Requirements.

As this Court held in *Feist*, Article I, Section 8, clause 8 of the Constitution imposes a threshold requirement of originality (sufficient creativity) for any grant of copyrights. "Originality is a constitutional requirement. . . . [In *The Trade-Mark Cases*, t]he Court explained that originality requires independent creation plus a modicum of creativity. . . . [In *Burrow-Giles*,] the Court emphasized the creative component of originality." *Feist*, 499 U.S. at 346

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[11] *Cf. Bilski*, 130 S. Ct. at 3226-27 ("the machine-or-transformation test is a useful and important clue. . . . [i]t is not the sole test for deciding") (citing, inter alia, *Benson*, 409 U.S. at 63). As the holding in *Bilski* suggests, the machine-or-transformation framework is no test at all. The Court did not rely on it, but rather analyzed the claims under the ineligible abstract idea-insignificant post-solution activity approach. *See id.* at 3231. The machine-or-transformation framework only invites artful claim drafting that adds no *inventive* creativity. *See, e.g., Benson*, 409 U.S. at 72. To avoid confusion, the Court in this case should disavow the machine-or-transform framework as a clue or test, and should mandate judicial and administrative use of the prior art treatment and creative application of ineligible discoveries approach.

(citing *The Trade-Mark Cases*, 100 U.S. 82, 94 (1879), and *Burrow-Giles Lithographic Co. v. Sarony*, 111 U.S. 53, 58 (1884)); *see* Paul J. Heald, *The Vices of Originality*, 1991 Sup.Ct. Rev. 143, 168-75 (Congress may not circumvent the originality requirement by protecting unoriginal works under the Commerce Clause).

Similarly, in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), this Court stated in regard to patents that Article I, Section 8, clause 8:

> is both a grant of power and a limitation. . . . to the promotion of advances in the 'useful arts.' . . . [The Congress may not] enlarge the patent monopoly without regard to the innovation, advancement or social benefit gained thereby. Moreover, Congress may not authorize the issuance of patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available.

Id. at 5-6; *see Great A. & P. Tea Co. v. Supermarket Equip. Co.*, 340 U.S. 147, 154-55 (1950) (Douglas, J., concurring) ("[E]very patent case involving validity presents a question which requires reference to a standard written into the Constitution. . . . It is not enough that an article is new and useful.").

Granting patents on insufficiently creative applications of new discoveries of science, nature and ideas will withdraw existent knowledge from the public domain constructed by the prior art treatment of ineligible discoveries. Given prior art treatment,

creativity in the application of ineligible discoveries is a constitutional requirement.[12]

Prior art treatment of ineligible discoveries is also a constitutional requirement. When the Constitution was enacted, there was a fundamental, widespread belief in a moral duty to create, preserve, and disseminate the public domain of science, nature, and ideas, which (in light of additional concerns over government created monopolies) limited the power granted to Congress to authorize exclusive patent rights *only* to "Inventors" for *their* "Discoveries." U.S. Const., art. I, § 8, cl. 8; *see Graham*, 363 U.S. at 5; Jefferson Letter, *supra*, at 531; *see generally* Giles S. Rich, *The Relationship Between Patent Practices and the Anti-Monopoly Laws*, 14 Fed. Cir. B.J. 5 (2004-2005) (1942); Harold G. Fox, Monopolies and Patents: A Study of the History and Future of the Patent Monopoly (1947). As this Court and lower courts have previously suggested, Congress lacks the power to grant copyrights or patents to those who are not

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[12] *See, e.g.*, Walterscheid, *Study*, *supra*, at 335-44 (discussing arguments for a qualitative invention standard in the Constitution); Edward C. Walterscheid, *The Hotchkiss Unobviousness Standard: Early Judicial Activism in the Patent Law*, 13 J. Intell. Prop. L. 103, 124-26 (2005) (hereinafter "Walterscheid, *Unobviousness*") (arguing that the Court in *Graham* interpreted the Constitution to impose a requirement of inventive creativity beyond novelty, but did not justify the specific requirement of obviousness on the Constitution).

"Authors" of "Writings" or "Inventors" of "Discoveries."[13] This moral duty and restriction on legislative power has been consistently effectuated by Congress, from the first Patent Act through the present. The duty should be understood to protect a fundamental, historical right of the public that may not be abridged by Congress.[14] As Thomas Jefferson reminisced, the

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[13] *See, e.g., Kewanee Oil Co.*, 416 U.S. at 476 (discussing "discovery" and "invention"); *Feist*, 499 U.S. at 346-47 (discussing "writings" and "authors"); *In re Kemper*, 14 F. Cas. 286, 287 (C.C.D. D.C. 1841) (No. 7,687) (" 'Invention differs from discovery.' . . . A discovery, in this sense, is not the subject of a patent; and it will be found, by a careful perusal of the constitution and laws of the United States upon the subject of patents for useful arts, &c., that it is not there used in this sense, but always as synonymous with invention.") (citation omitted); Giles S. Rich, *Laying the Ghost of the "Invention" Requirement*, 1 APLA Q.J. 26, 29-34 (1972-73) (hereinafter "Rich, *Laying the Ghost*") (noting that a qualitative "invention" requirement is reflected in the Constitution's restriction to "Inventors"); Albert H. Walker, Text-book of the Patent Laws of the United States of America 2 (2d ed. 1889) ("The word 'discovery' does not have, either in the Constitution or the statute, its broadest signification. It means invention, in those documents, and in them it means nothing else."); *cf. Mazer v. Stein*, 340 U.S. 201, 220-21 (1954) (Douglas, J., concurring) ("Perhaps these are all 'writings' in the constitutional sense. But to me, at least, they are not obviously so. It is time that we came to the problem full face.").

[14] *Cf. District of Columbia v. Heller*, 554 U.S. 570, 592 (2008) ("This meaning is strongly confirmed by the historical background of the . . . Amendment. We look to this because it has always been widely understood that the . . . Amendment . . . codified a *pre-existing* right."); *Borough of Duryea, Pa. v. Guarnieri*, 131 S. Ct. 2488, 2503 (2011) ("The reference to 'the right of the people' indicates that the Petition Clause was

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1790 Patent Board had adopted exclusions for uncreative new uses of pre-existing things shortly after the Constitution was ratified, as otherwise patent rights would "take" this right to free benefit from the public "and give [it] to a monopolist." Jefferson Letter, *supra*, at 531; *cf. Burrow-Giles*, 111 U.S. at 57 ("The construction placed upon the Constitution by the first act of 1790 . . . is . . . entitled to very great weight.").

In sum, this Court should declare that the Constitution requires both prior art treatment and the exclusion from eligibility of discoveries of science, nature, and ideas, which creates a public domain of pre-existing and fundamental information and things. This also implies a constitutional requirement for "invention" to reflect creativity in the application of excluded discoveries, without which patents impermissibly withdraw useful knowledge from this public domain.

II. Consistent with the Constitution, the Patent Act Excludes under Section 101 Claims to Uncreative Applications of Ineligible Discoveries.

Since the first Patent Act of 1790, ch. 7, 1 Stat. 109 (Apr. 10, 1790), the Patent Board (later the Patent Office), the Congress, and the courts have excluded from "inventions" uncreative applications of

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intended to codify a pre-existing individual right, which means that we must look to historical practice to determine its scope.").

ineligible discoveries. The Court here should continue to construe the Patent Act to exclude such uncreative applications under Section 101.

A. The Patent Act Has Been Consistently Construed to Require Creativity in the Application of New Discoveries.

In the 1793 Act, Congress confirmed the approach adopted by the Patent Board under the 1790 Act, excluding from "discovery" any simple change "to the form or proportions" of two of the recognized statutory classes of subject matter. Patent Act of 1793, ch. 11, § 2, 1 Stat. 318, 321 (Feb. 21, 1793). Under that Act, lower courts confirmed the exclusions for discoveries and the requirement for additional inventive creativity, including for new uses. *See, e.g., Lowell*, 15 F. Cas. at 1019; *Howe*, 12 F. Cas. at 658.

In the 1836 Patent Act, Congress removed the statutory language regarding changes to form. *See* Patent Act of 1836, ch. 357, § 6, 5 Stat. 117, 119 (July 4, 1836). But this Court continued to construe the statute to exclude such changes and new uses. "'If it is old and well known, and applied only to a new purpose, that does not make it patentable.'" *Le Roy*, 55 U.S. (14 How.) at 177 (quoting *Bean v. Smallwood*, 2 F. Cas. 1142 (C.C.D. Mass. 1843) (No. 1,173)). The Court reiterated that creativity in the application, or substantial novelty, was required. *See* Edward C. Walterscheid, *Novelty and the* Hotchkiss *Standard*, 20 Fed. Cir. B.J. 219, 227-28 (2010) (citing cases);

Walterscheid, *Unobviousness, supra*, at 110 (citing Kenneth J. Burchfiel, *Revising the "Original" Patent Clause: Pseudohistory in Constitutional Construction*, 2 Harv. J.L. & Tech. 155, 191-95 (1989)).

In the 1870 Act, Congress did not make any relevant change to the eligibility requirements, preserving the Court's interpretations of the limits of "invention." *See* Patent Act of 1870, ch. 230, § 24, 16 Stat. 200 (July 8, 1870). The Court reiterated these requirements and articulated the non-analogous use standard for distinguishing eligible inventions from ineligible mere applications of new discoveries. *See Ansonia Brass & Copper Co.*, 144 U.S. at 18. The Court in *Funk Brothers Seed Co.* reaffirmed the ineligibility of uncreative applications of ineligible discoveries shortly before Congress adopted the 1952 Patent Act. *See* 333 U.S. at 130.

B. The 1952 Patent Act Preserved the Requirement for Inventive Creativity in Section 101.

In Section 101 of the Patent Act of 1952, Pub. L. No. 82-593, 66 Stat. 792 (July 19, 1952), Congress retained the structure, categories, and relevant language of the eligibility provision of the 1870 Act, with two exceptions: changing "art" to "process" and expanding the definition of a process (discussed in the

next section).[15] Specifically, Section 101 provides that "[w]hoever *invents or discovers* any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101 (2006) (emphasis added). Congress thus reiterated in Section 101 of the 1952 Patent Act that patent eligibility requires "invent[ion]s or discover[ie]s" as they were previously understood. *See Alappat*, 33 F.3d at 1553 (Archer, C.J., dissenting) ("The requirement of the patent law that an invention or discovery reside in the *application* of an abstract idea, law of nature, principle, or natural phenomenon is embodied in the language of 35 U.S.C. § 101") (emphasis in original). The patentability criteria similarly refer to "invention[s]," which are determined under Section 101. *See* 35 U.S.C. §§ 102, 103(a), 112, para. 1 (2006).

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[15] *See* H.R. Rep. No. 82-1923, at 6 (1952) (the language of the 1870 Act "has been preserved except that the word 'art' which appears in the present statute has been changed to the word 'process.' . . . The definition of 'process' has been added in Section 100 to make it clear that 'process or method' is meant, and also to clarify the present law as to the patentability of certain types of processes or methods as to which some insubstantial doubts have been expressed."); *id.* at 17 ("The remainder of the definition clarifies the status of processes or methods which involve merely the new use of a known process, machine, manufacture, composition of matter, or material; they are processes or methods under the statute and may be patented provided the conditions for patentability are satisfied."); Pasquale J. Federico, *Commentary on the New Patent Act*, 75 J. Pat & Trademark Off. Soc'y 161, 176-78 (1993) (1954).

The legislative history also indicates that Congress intended to re-codify the law and to preserve earlier judicial constructions of it,[16] making only two significant changes to the statute – *i.e.*, creation in Section 103 of a new "nonobviousness" standard (discussed further below), and changing the law on contributory infringement. *See* H.R. Rep. No. 82-1923, at 5 ("incorporating a requirement for invention in § 103"). Congress thus recognized and codified *both* in Section 101 (to distinguish ineligible discoveries and insufficiently creative applications of them) and in Section 103 (to evaluate creativity for prior art defined under Section 102, which does not include such discoveries unless previously disclosed) the historic requirement for *invention*. *See* 35 U.S.C. § 101 ("invents or discovers"); 35 U.S.C. § 103(a) ("though the *invention* is not identically disclosed or described as set forth in Section 102") (emphasis added). In doing so, Congress codified and preserved the categorical exclusions from eligibility, their prior art treatment, and the requirement for creativity in their application.

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[16] *See* H.R. Rep. No. 82-1923, at 2, 3 ("Since the sections of the Revised Statutes relating to patents were merely a compilation of the act of July 8, 1870, our present patent law is essentially the act of 1870 with subsequent amendatory and supplemental enactments. . . . [T]he purpose of the bill is to revise and codify the laws relating to patents and enact into law title 35 of the United States Code entitled 'patents' ").

C. Sections 100(b) and 103 Did Not Alter Section 101's Requirement for Creativity in the Application.

In enacting a definition of "process" in Section 100(b), Congress intended to modify only one aspect of the earlier eligibility requirements for "invention," and did so for only one of the statutory classes of invention. *See* 35 U.S.C. § 100(b) (2006) ("The term 'process' . . . includes a new use of a known process, machine, manufacture, composition of matter, or material."). It could not, therefore, have intended to modify generally the requirement for invention codified in the "invents or discovers" language of Section 101. 35 U.S.C. § 101. As the legislative history noted, "[t]he definition of process has been added . . . to clarify the present law as to the patentability *of certain types of processes or methods* as to which some insubstantial doubts have been expressed." H.R. Rep. No. 82-1923, at 6 (emphasis added). These doubts were based on *In re Thuau*, 135 F.2d 344, 347 (C.C.P.A. 1943), which had held that *no* new uses were eligible as inventions. In authorizing new uses to qualify as process inventions, Congress intended to restore the law of invention to where it had been established by this Court in *Ansonia Brass & Copper Co.*[17] Had Congress intended the more fundamental

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[17] *See, e.g.*, Stefan A. Reisenfeld, *The New United States Patent Act in the Light of Comparative Law I*, 102 U. Penn. L. Rev. 291, 299-300 (1954) ("[T]he background of the amendment gives reason to assume that a newly discovered use for a known substance, machine or process is still only patentable if it is not

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changes of authorizing patents for all new uses, altering prior art treatment of new discoveries, and eliminating the requirement for creativity in the application, it certainly would have said so.

Similarly, Congress in 1952 adopted the new terminology of "non-obvious subject matter" in Section 103 to codify the *Hotchkiss* creativity requirement and to reverse earlier decisions by this Court regarding the kind and threshold of creativity required for invention. *See* H.R. Rep. No. 82-1923, at 7 ("That provision paraphrases language which has often been used in decisions of the courts, and the section is added to the statute for uniformity and definiteness. This section should have a stabilizing effect and minimize great departures which have appeared in some cases."); *id.* at 18 ("[T]he refusal of patents by the Patent Office, and the invalidation of patents by the courts, on the ground of *lack of invention* or lack of patentable novelty has been followed since at least as early as 1850. This paragraph is added with the view that an explicit statement in the statute may have some stabilizing effect. . . .")

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merely analogous or cognate to the uses heretofore made. . . . [I]t is fair to state that in essence the new statutory definition of 'process' restores the broad principles of patentability flowing from a careful analysis of the exposition given by the Supreme Court in the *Ansonia* case."); Federico, *supra*, at 177-78 ("The reference to the new use of a known machine or manufacture in the definition merely means that processes may utilize old machines or manufactures and the reference to the new use of a known process simply indicates that the procedural steps in a patentable process might be old.").

(emphasis added). In doing so, Congress also could not have intended the much broader changes of eliminating the exclusions for discoveries, their prior art treatment, and the requirement for creativity in their application. As this Court later held in *Graham*, Congress did not seek to change the law regarding the degree of inventive creativity.

> The major distinction is that Congress has emphasized "nonobviousness" as the operative test of the section, rather than the less definite "invention" language of *Hotchkiss* that Congress thought had led to "a large variety" of expressions in decisions and writings.
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> It is undisputed that this section was, for the first time, a statutory expression of an additional requirement for patentability, originally expressed in *Hotchkiss*. It also seems apparent that Congress intended by the last sentence of § 103 to abolish the test it believed this Court announced in the controversial phrase "flash of creative genius," used in *Cuno Engineering Corp. v. Automatic Devices Corp.*, 314 U.S. 84. . . . (1941).
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> . . . .
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> We believe that this legislative history, as well as other sources, shows that the revision was not intended by Congress to change the general level of patentable invention.

383 U.S. at 14, 15, 17.

In sum, when adopting new terminology and creating an explicit requirement for non-obviousness in Section 103, Congress codified in rather than eliminated from Section 103 the requirement for an eligible invention as determined under Section 101. *See* 35 U.S.C. § 103(a) ("though the *invention*") (emphasis added). Construing the statute to have eliminated the historic exclusions, their prior art treatment, or the requirement for creativity in their application would raise serious constitutional questions. These questions should be avoided. *See Gomez v. United States*, 490 U.S. 858, 864 (1989); *Ashwander v. Tennessee Valley Auth.*, 297 U.S. 288, 346-48 (1936).

Efforts by Judge Rich to recast the legislation, moreover, are simply unavailing. *See, e.g.*, Rich, *Laying the Ghost, supra*, at 29 ("we have *not* had [the 'requirement for invention'] for the past twenty years. Instead, we have § 103."). But even if Judge Rich had been correct, there would be no point to preserving as *eligible* inventions under Section 101 uncreative claims applying ineligible science, nature and ideas. Given prior art treatment, such claims will *necessarily* be obvious and thus *unpatentable* under Section 103.

III. Threshold Exclusion under Section 101 Is Critical Here.

It is critically important for the Court to employ Section 101 in its traditional "threshold" role in determining whether an eligible invention has been

created, by applying prior art treatment to ineligible discoveries and by requiring creativity in their application. *Bilski*, 130 S. Ct. at 3225; *see Diehr*, 450 U.S. at 189-90 (noting that Section 101 decisions on eligibility are separate from determinations of the "conditions and requirements" of patentability, which include obviousness under Section 103). This case illustrates why. Absent prior art treatment of the new discovery at issue, the claims here might improperly survive scrutiny under patentability criteria. Given prior art treatment, threshold exclusion under Section 101 is efficient, as uncreative claims applying ineligible discoveries will necessarily fail under less efficient patentability evaluations for Section 103 obviousness. Threshold exclusion under Section 101, moreover, signals that the public domain is off-limits and thereby directs investment and activity towards creative, and potentially patentable, inventions.

A. Without Prior Art Treatment, the Claims at Issue May Improperly Survive Scrutiny Under Sections 101, 102, 103, and 112.

Without treating the new discovery of the particular, correlated levels of the metabolites at issue as prior art, the claims here might improperly survive scrutiny under Sections 101, 102, 103, and 112. First, the claims are clearly directed to physical activity (*e.g.*, "administering a drug" and "determining" a level of the drug) that would qualify as a statutory process but for the exclusion of ineligible discoveries,

prior art treatment, and the requirement for creativity in their application. U.S. Pat. No. 6,680,302, claim 1 (filed Dec. 27, 2001) (hereinafter "'302 Patent"); *see* 35 U.S.C. § 101; *Bilski*, 130 S. Ct. at 3225-26 (interpreting "'process'" broadly except by reference to the exclusions for science, nature, and ideas). Assuming for argument that these claims are in fact new by requiring some new, human recognition of the discovered correlation reflected in measured values,[18] they also are useful, practical applications of an ineligible discovery (albeit less useful than if the claim required some action following recognition). *See* 35 U.S.C. § 101 ("new and useful . . . process"). The only novelty would then exist in the recognition step, which is clearly an uncreative application of the *scientific* creativity reflected in the ineligible biological discovery, and the other steps are insignificant, post-solution activities. Without the requirement for creativity *in the application*, the claims might improperly survive under Section 101.

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[18] The "wherein" steps of Claim 1 of the '302 patent and other claims require only that "the level" of the measured drug (or metabolite) "indicates a need." '302 Patent, claim 1. The administration step and the measuring step for the particular drug were part of the prior art, as was adjusting the dosage based on measurement and recognition of some relationship between measured levels and clinical efficacy and tolerance. *See* Petition for a Writ of Certiorari, Mayo Collaborative Servs. v. Prometheus Labs, Inc., No. 10-1150, at 4-5 (S. Ct. Mar. 17, 2011) (citing sources). Thus, unless "indicates" is construed to require recognition of the discovered correlation, the claims are not new, as the "indicat[ion]" existed in the prior art.

Similarly, without prior art treatment of the ineligible discovered correlation, the claims might improperly be found to be novel inventions under Section 102. The correlation itself would be inherent to any prior art measurements of the metabolite levels, but *recognition* of the correlation (and the benefits that might flow from recognition) may not have occurred before the discovery. *See, e.g.*, Dan L. Burk & Mark A. Lemley, *Inherency*, 47 Wm. & Mary L. Rev. 371, 374-81 (2005) (discussing the requirement of public benefit for finding inherency).

Without prior art treatment, the claims also might improperly be found non-obvious under Section 103. Nothing in the prior art may have provided a "teaching, suggestion, or motivation" to discover and recognize the *specific* correlation. *KSR Int'l. Co. v. Teleflex, Inc.*, 550 U.S. 398, 418 (2007). Biology is unpredictable and it may not have been obvious to try to discover and apply the correlation. *See id.* at 419-21. Nevertheless, a general relationship between dose, efficacy, and tolerance has been known since Paracelsus. *See, e.g.*, W. Norman Aldridge, Mechanisms and Concepts in Toxicology 137 (1996). And once the discovered correlation is treated as prior art, recognizing what it indicates is truly trivial.

Finally, the claims might improperly be found to be adequately described and enabled. *See* 35 U.S.C. § 112, para. 1. The specification discloses the newly discovered correlation, the present benefits of applying it in the process, and the method of performing the process in a manner that those skilled in the art

(and probably those who are not) can readily perform.[19] The claims may therefore be found patentable, while lacking any *inventive* creativity. Further, the claims are specific and concrete applications of the discovery, and may not overreach the applicant's *scientific* contribution to the art. *Cf. Ariad*, 598 F.3d at 1353-54 (written description "'ensure[s] that the scope of the right to exclude . . . does not overreach the scope of the *inventor's* contribution to the field of art. . . .'") (citation omitted and emphasis added). But the claims may preempt all practical applications of the ineligible discovery.

Even if the claims preempted only a limited range of uncreative applications, they would constrict the public domain of such discoveries. When disclosed in the patent's specification, discoveries like the correlation at issue are supposed to become public domain information, freely available for immediate use (even without regard to prior art treatment). *See, e.g., Ariad*, 598 F.3d at 1359 (Newman, J., additional views) ("The written description is the way by which the scientific/technologic information embodied in

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[19] *See, e.g., Consolidated Electric Light Co. v. McKeesport Light Co.*, 159 U.S. 465, 474 (1895) ("independent experiment" standard for lack of enablement); *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1350-52 (Fed. Cir. 2010) (en banc) ("possession," "actually invented," or "'visualize or recognize'" standard for adequate written description) (citation omitted); *cf. In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988) ("undue experimentation" standard for lack of enablement).

patented inventions is disseminated to the public, for addition to the body of knowledge and for use in further understanding and advance."). But such claims to uncreative applications only restrict the use of discoveries for further understanding, invention, and benefit.

In sum, without prior art treatment of ineligible discoveries and the requirement for creativity in their application, the claims at issue might improperly be found eligible and patentable and would constrict the public domain.

B. With Prior Art Treatment, The Claims At Issue Will Necessarily Fail Both Section 101 Eligibility Analysis and Less Efficient Section 103 Patentability Analysis.

By its own terms, Section 103 requires a non-obvious "invention," as defined under Section 101. *See* 35 U.S.C. § 103. There is no inventive creativity in merely applying the new discovery using the prior art method. The correlation at issue requires these conventional, preparatory steps for its recognition; they are merely "token, post-solution components" in the claimed process. *Bilski*, 130 S.Ct. at 3231. *See In re Grams*, 888 F.2d 835, 839 (Fed. Cir. 1989) (given the ineligibility of algorithms, "it follows that the addition of the old and necessary antecedent steps of establishing values for the variables in the equation cannot convert the unpatentable method to

patentable subject matter.") (quoting *In re Christensen*, 478 F.2d 1392, 1394 (C.C.P.A. 1973)).[20] The claims are ineligible, and without invention are unpatentable.

Even if Section 103 did not require "invention," with prior art treatment such uncreative claims applying ineligible discoveries will *necessarily* be obvious and thus unpatentable under Section 103. *See, e.g., Dann v. Johnston*, 425 U.S. 219, 220 (1976) (reiterating the need to evaluate the differences between the prior art and the claim). The ineligible discovery itself "teach[es], suggest[s], or motivat[es]" the combination with these preparatory steps. *KSR Int'l. Co.*, 550 U.S. at 418, 420.

Preserving the eligibility of such claims under Section 101 only to reject them later under more complex Section 103 patentability evaluations is inefficient. Obviousness decisions under Section 103 are supposed to be made after searching for prior art under Section 102 and by engaging in extensive factual investigations that consider the ability of

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[20] This would be true even if the preparatory steps were not part of the prior art, or if the claims were to require someone to take action after recognizing the correlation. The fact that the claims would require or result in physical transformations would not supply eligibility and would not prevent the claims from being obvious, as even lay patients would have the common sense to perform the preparatory steps. *See, e.g., Lab. Corp. of Am. Holdings*, 548 U.S. at 138 (noting both restrictions on claim scope and physical transformations required to perform the challenged process); *KSR Int'l. Co.*, 550 U.S. at 418.

skilled persons in the relevant art. *See* 35 U.S.C. § 103(a); *Graham*, 383 U.S. at 17-18. In contrast, ineligibility decisions under Section 101 should be apparent on the face of the patent, as the new discovery and how it is being applied will normally be described by the applicant (and may need to be described to meet the requirements of Section 112, paragraph 1). *See* 35 U.S.C. §§ 101, 112, para. 1. It will be comparatively easy to make a threshold eligibility determination of what (if any) *inventive* creativity is reflected in the claims beyond mere application of a new discovery. *Cf. Diehr*, 450 U.S. at 188-89; *id.* at 213 (Stevens, J., dissenting). Preserving uncreative claims for further evaluation under Section 103 only wastes scarce administrative resources. *Cf.* Michael J. Meurer, *Patent Examination Priorities*, 51 Wm. & Mary L. Rev. 675, 704 (2009) (suggesting four ways to tailor scarce examination resources).

Worse yet, preserving the eligibility of such claims under Section 101 invites administrative errors under Section 103. Such claims erroneously may be found non-obvious absent prior art treatment. *See supra*. So far, there is no explicit precedent for prior art treatment of ineligible discoveries under Section 103, although "invention" is required. Further, before this Court's decision in *KSR Int'l. Co.*, even with prior art treatment such claims may wrongly have been found to be non-obvious. New discoveries may not themselves provide an *explicit* teaching, suggestion, or motivation for their own uncreative, limited applications. *See* 550 U.S. at 418.

Here, the discovery of the correlation would not explicitly suggest combining the "wherein . . . indicates" step reflecting the newly discovered correlation with the prior art administering and determining steps, although no creativity is required to do so. '302 Patent, claim 1. Even after *KSR International Co.*, mistakes regarding obviousness still happen all too frequently. *See, e.g.*, Yi-Chen Su, *What About Know-How: Heightened Obviousness and Lowered Disclosure is Not a Panacea to the American Patent System for Biotechnology Medication and Pharmaceutical Inventions in the Post-KSR Era*, 14 Marq. Intell. Prop. L. Rev. 321, 363 (2010).

So long as the discovery continues to be treated as prior art, claims like those at issue here will be ineligible and will necessarily be obvious. This Court should bar such claims at the threshold under Section 101.

C. Threshold Exclusion under Section 101 Signals that the Public Domain is Off Limits to the Patent System.

As recognized by Justice Breyer in *Laboratory Corp. of America Holdings*, allowing patents for uncreative applications of science, nature, and fundamental information imposes severe social costs. *See* 548 U.S. at 128. Threshold exclusion under Section 101 makes clear that such basic information is part of the public domain and is off-limits to patenting. The patent system exists to reward inventive creativity,

not creative claim drafting that restricts free access to pre-existing or fundamental information and things.

Signaling these limits on the patent system has numerous social benefits. The exclusions for science, nature, and ideas under Section 101 identify the need for public funding of scientific discovery. The eligibility requirement for creativity in the application (and the prohibition on claiming insignificant post-solution activity) helps to avoid futile patent applications and signals to investors and inventors that they should direct their funds and activity towards more creative applications of new scientific, natural, and abstract discoveries. *Cf., e.g.*, John H. Barton, *Non-Obviousness*, 43 IDEA 475, 492 (2003) ("at least up to a point, the dynamic benefits of strengthening the non-obviousness standards outweigh the static costs"). Affirming and clarifying these requirements will enhance these benefits.

CONCLUSION

For the foregoing reasons, the Court should affirm the District Court's rejection of the patent claims at issue, hold that prior art treatment of ineligible discoveries of science, nature, or ideas is a constitutional requirement, and reaffirm that patent eligibility ("invention") requires creativity in the application of any such discoveries.

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-1150

IN THE
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES (D/B/A MAYO MEDICAL LABORATORIES) AND MAYO CLINIC ROCHESTER,

Petitioners,

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PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR *AMICUS CURIAE* NOVARTIS CORPORATION SUPPORTING RESPONDENT

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QUESTION PRESENTED

Whether the Federal Circuit correctly held that concrete methods for improving the treatment of patients suffering from autoimmune diseases by using individualized metabolite measurements to inform the calibration of the patient's dosages of synthetic thiopurines are patentable processes under 35 U.S.C. §101.

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PROMETHEUS LABORATORIES, INC.,

Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF FOR *AMICUS CURIAE* NOVARTIS CORPORATION SUPPORTING RESPONDENT

INTEREST OF *AMICUS CURIAE*

Novartis Corporation ("Novartis") is an indirect wholly-owned subsidiary of Novartis AG, a Swiss holding company,[1] whose affiliates around the world provide

[1] Pursuant to this Court's Rule 37.6, *amicus* affirms that no counsel for a party authored this brief in whole or in part, that no such counsel or party made a monetary contribution intended to fund the

healthcare solutions that address the evolving needs of patients and societies. Novartis is a U.S. holding company which owns, directly or indirectly, several of Novartis AG's subsidiaries and affiliates. Focused solely on healthcare, the Novartis companies offer a diversified portfolio to best meet patient and social needs: innovative medicines, eye-care products, cost-saving generic pharmaceuticals, preventive vaccines, diagnostic tools, over-the-counter health aids, and animal-health products.

Novartis has considerable interest in this case. Like any healthcare company, Novartis relies on patents to protect its many innovations in patient care. Absent an ability to protect its investments with valid patents, healthcare companies like Novartis would lack the necessary incentive to make the extraordinary financial outlays required to bring medical innovations to market.

A reversal of the judgment below would threaten the patent-eligibility of therapeutic and diagnostic processes under §101 of the Patent Act, 35 U.S.C. §101. This would have a chilling effect on the advancement of the healthcare solutions developed by the Novartis companies and others. In turn, this would have a devastating impact on those who depend on such developments (and on the investments which make those developments possible) for their health and for the support of their local economies.

SUMMARY OF ARGUMENT

Section 101 of the Patent Act has an intentionally and historically broad scope. This Court has repeatedly affirmed that breadth and never has held that medical diagnostic or therapeutic processes are categorically ineli-

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preparation or submission of this brief, and that no person or persons other than *amicus* and its counsel made such a monetary contribution. Both parties have consented to the filing of this brief. The parties' letters so consenting have been filed with the Clerk's office.

gible for protection under that section. It should decline Mayo's invitation to break from that tradition now.

Medical therapeutic techniques and medical diagnostic methods often employ the detection of biomarkers (DNA sequences or other biological substances) to guide a diagnosis or a course of treatment.[2] Such biomarker-based claims create the possibility of genuinely personalized medicine, *i.e.*, individualized patient care tailored to a patient's unique biological profile, including his or her genetic makeup. Traditional medicine situates a patient within broad averages, and therefore assumes that each patient will respond according to the mean. But personalized medicine uses biomarkers to correlate an *individual's* genetic makeup with particular diseases; to identify whether the *individual* will be compatible with particular therapies that work for some, but not all, patients; or to pinpoint the dosage range over which a therapy will exhibit a combination of maximal efficacy and safety for the *individual*.

Those techniques—new and infinitely useful—are processes that are patent-eligible under §101. They lie squarely within the "useful arts" that delineate that section's broad and dynamic scope. See *In re Bergy*, 596 F.2d 952, 958 (C.C.P.A. 1979), *aff'd sub. nom. Diamond* v. *Chakrabarty*, 447 U.S. 303 (1980); see also *J.E.M. Ag Supply, Inc.* v. *Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 135 (2001); *Bilski* v. *Kappos*, 130 S. Ct. 3218, 3236 (2010) (Stevens, J., concurring in judgment). Indeed, these new

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[2] Representative language for the therapeutic-method claims in this case can be found at Pet. App. 4a-5a. Representative language for a diagnostic-method claim includes: "a method for diagnosing disease X in a human patient comprising detecting in a sample taken from such patient the presence of sequence Y in gene Z, wherein the presence of sequence Y in gene Z indicates the likelihood of developing disease X."

techniques are directed to perhaps the most "useful" endeavor of all—directly enhancing the quality of, or even sustaining the very existence of, human life.

To be sure, therapeutic- and diagnostic-process claims invariably hinge on laws of nature, which themselves are not patentable and, hence, belong equally to all.[3] But such claims, to be valid, do more than simply inscribe natural laws. Rather, they invariably *use* such laws to solve otherwise intractable problems relating to patient diagnosis and treatment. As this Court has repeatedly held, processes *applying* laws of nature, natural or physical phenomena, or abstract ideas are patent-eligible under §101, because they do not *preempt* these fundamental principles of science. See *Bilski*, 130 S. Ct. at 3230 (quoting *Diamond* v. *Diehr*, 450 U.S. 175, 188 (1981)).[4]

Granted, the problem of meritless claims securing patent protection is real. It largely motivated Justice Breyer's dissent in *Laboratory Corp. of America Holdings* v. *Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) ("*Lab. Corp.*"). Had the Court not dismissed the case, Justice Breyer would have held a diagnostic-process claim, directed to assaying a body fluid for elevated homocysteine levels and correlating those elevated levels with a deficiency in cobalamin or folate, to be "an unpat-

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[3] Although the "laws of nature" and "natural or physical phenomena" exceptions to §101 may be technically separate, they are treated as analytically indistinct for purposes of this brief. When referring to the conceptual space occupied by both the "laws of nature" and "natural or physical phenomena" exceptions, this brief refers for convenience to "the laws of nature."

[4] Novartis also filed a brief as *amicus curiae* in *Bilski*. Many of the arguments in that brief are highly relevant to the Court's resolution of this case. As appropriate, and as modified to reflect the differences between the two cases, those arguments are raised here as well.

entable 'natural phenomenon.'" *Id.* at 132-134, 138 (Breyer, J., dissenting from dismissal of certiorari). But this conclusion must be seen in the context of the unique procedural history of that case, under which infringement turned solely on whether the accused infringer performed the claim's "correlating" step. This distorted the scope and meaning of the claim for purposes of the §101 analysis, generating the dissent's understandable—but incorrect—impression that the claim preempted a natural law. In fact, the claim only preempted the use of the natural law in facilitating a diagnosis and treatment of specific vitamin B deficiencies, which is permissible.

Moreover, Justice Breyer's *Lab. Corp.* proposal to render the claim-at-issue patent-ineligible under §101 would have aggrandized the role of §101 at the expense of other provisions of the Patent Act. Sections 102, 103, and 112, in particular, are powerful filters in their own right for preventing meritless claims from becoming patentable. Congress intended to address many of the concerns motivating Justice Breyer's dissent not under the coarse filter of §101, but with precision, based on the exacting conditions of patentability recited in sections such as §§102, 103, and 112.

Asking §101 to do the work of those sections is to propose an answer that is far worse than the problem. It would force a procrustean solution on the courts and the country. It would disregard the text and structure of the Patent Act, which encourages the kind of innovation, investment, and activity that leads to the development of the useful arts. With the stroke of a pen, it would decree that diagnostic and therapeutic innovations, which are the fruits of immense financial and intellectual investment, are *not* patent-eligible. Doing so would have the readily foreseeable and undesirable consequence of depriving American patients of much-needed medical inno-

vation and the American economy of much-needed activity.

This case provides an opportunity to ensure that the scope of §101 is properly calibrated. Because the judgment below properly respects that section's boundaries and its role within the Patent Act, this Court should affirm that judgment.

ARGUMENT

THERAPEUTIC- AND DIAGNOSTIC-PROCESS CLAIMS ARE PATENT-ELIGIBLE UNDER §101

This case presents another opportunity for the Court to address the patent-eligibility of process claims under 35 U.S.C. §101. In *Bilski*, the last case considering the scope of §101, the Court rejected a rigid "machine-or-transformation" test, holding that such a rule did not trace the outer limits of §101. 130 S. Ct. at 3231. Nevertheless, the Court found the claims-at-issue—methods for transactional risk-hedging—not to be patent-eligible since they were merely directed to an abstract idea. *Ibid.*

This case raises the different question of whether certain therapeutic-process claims are impermissibly directed to a law of nature. More particularly, respondent's process claims are directed to determining whether a particular class of drugs is being administered to an individual patient at a safe and efficacious dose, and then using that determination to guide the dose at which that drug will be subsequently administered to the patient. Petitioner asserts that these claims, in essence, impermissibly preempt a natural phenomenon, namely a correlation between the levels of a drug's metabolite (the biomarker) in a patient and the efficacy and safety of the administered drug. The Federal Circuit properly held that the claims are not directed to such impermissible subject matter, but are directed to a particular *applica-*

tion of that correlation, which §101 permits. Pet. App. 14a.

The key distinction between unpatentable laws of nature, and patentable applications of such laws, was central to the dispute in *Lab. Corp.*, which the Court was asked to consider five years ago. The claim at issue in *Lab. Corp.*, like the claims at issue here, is based on detecting a biomarker. The claims in both cases *apply* a natural correlation, in one instance to determine and ensure that a drug is dosed correctly (*Prometheus*) and the other to diagnose disease (*Lab. Corp.*). The Court left the patentability question unresolved in *Lab. Corp.*, concluding that the issue had not been properly preserved for review. Justice Breyer (joined by Justices Stevens and Souter) dissented. Justice Breyer would not have dismissed the case, and would have resolved it by holding that the claimed process for detecting vitamin B deficiencies was "an unpatentable 'natural phenomenon.'" 548 U.S. at 138 (Breyer, J., dissenting from dismissal of certiorari).

The Court should not resolve this case by adopting the views expressed in the *Lab. Corp.* dissent. The concerns that motivated the dissent are real: Substantively unworthy inventions or discoveries should not receive patent protection. But sections of the Patent Act other than §101 (particularly §§102, 103, and 112) are fully capable of addressing those concerns. Constricting §101 so tightly that therapeutic- and diagnostic-method claims would be summarily precluded from patent-eligibility would not only usurp the filtering function of these other sections of the Patent Act, but also effectively invalidate a plethora of patents directed to such subject matter. Furthermore, it would endanger the pharmaceutical and biotechnology industries, patients throughout the United States, and the American economy. Indeed, denying patent protection would retard the unfolding revolution in

healthcare stimulated in large part by personalized medicine. Without the promise of patent protection, the necessary incentive to make the intensive and costly investment in the research and development of therapeutic and diagnostic processes would instantly disappear, as would the benefits such an investment provides to our economy.

The text of §101 and the structure of the Act command no such result. The Court should therefore affirm that the claims at issue in this case, like the one at issue in *Lab. Corp.*, are directed to *applications* of natural phenomena and, as such, are patent-eligible under §101.

A. Section 101 has a broad scope and is counterbalanced by other sections of the Patent Act

This Court has recognized that Congress purposefully worded §101 broadly so that it would be "given wide scope," *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 308), and, in turn, ensure that "'ingenuity [would] receive a liberal encouragement.'" *Ibid.* (quoting *Chakrabarty*, *supra*, at 308-309 (quoting 5 Writings of Thomas Jefferson 75-76 (H. Washington ed. 1871)). Indeed, §101 is a coarse filter that defines what subject matter is eligible for patent protection. Consistent with that function, it ensures that basic principles of science are available to everyone and not removed from the public domain. This Court has recognized that Congress intended the Patent Act to authorize the patenting of "anything under the sun that is made by man," *Diehr*, 450 U.S. at 182, so long as the subject matter sought to be claimed otherwise met "the conditions and requirements of [the Act]," §101.

This perspective has undergirded the Court's holdings of patent-eligibility for a diverse array of subject matter, ranging from a directional antenna system in which the wire arrangement was determined by the logical application of a mathematical formula, see *Mackay Radio & Tel.*

Co. v. *Radio Corp. of Am.*, 306 U.S. 86 (1939), to organisms genetically engineered to break down crude oil, see *Chakrabarty*, 447 U.S. 303. Beyond the necessity of falling within a recognized class of invention (*i.e.*, a process, machine, manufacture, or composition of matter), the only restrictions on the broad reach of §101 are the prohibitions against claiming "'laws of nature, physical [or natural] phenomena, and abstract ideas.'" *Bilski*, 130 S. Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 309). Those subjects are attributable to no inventor and, being in the nature of fundamental tools of science, belong equally to all.

Yet even those exclusions have their limitations. Process claims involving such laws of nature, natural phenomena, or abstract ideas *are* patent-eligible if the claims are to a new and useful *application* of those laws, phenomena, or ideas. *Bilski*, 130 S. Ct. at 3230 (citing *Diehr*). Other decisions by this Court make the same point: "'He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly *of it* which the law recognizes. If there is to be invention from such a discovery, it must come from the *application* of the law of nature to a new and useful end.'" *Gottschalk* v. *Benson*, 409 U.S. 63, 67 (1972) (quoting *Funk Bros. Seed Co.* v. *Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) (emphasis added)).

This Court's precedents thus establish a bright-line test, namely that one may not patent a law of nature itself, but may patent an *application* of it for "new and useful" ends. This should not be viewed as an unusual balance to strike; virtually any useful patent claim must ultimately rely on laws of nature to generate useful results. As articulated in more detail in Section B, *infra*, diagnostic-process claims, like the therapeutic-process claims at issue here, are not simply directed to a law of nature itself, but to a practical application of a law. They

invariably require the detection of a biomarker and take advantage of a natural correlation between that biomarker and a disease to make a diagnosis and thereby inform a course of treatment, if needed or desired. Hence they do not offend §101.

This does not minimize or trivialize the legitimate and important concerns expressed in the *Lab. Corp.* dissent and the concurring opinion authored by Justice Stevens in *Bilski*. Those concerns underscore the need for proper safeguards to weed out meritless patents. If "anything under the sun" or any series of steps or way of doing something can be patented, that overabundance can create genuine inefficiencies and unfairness. Sometimes "'*too much* patent protection can impede rather than "promote the Progress of . . . useful Arts,'" the constitutional objective of patent and copyright protection. *Bilski*, 130 S. Ct. at 3255 (Stevens, J., concurring in judgment) (quoting *Lab. Corp.*, 548 U.S. at 126-127 (Breyer, J., dissenting)) (emphasis in original).[5]

One can agree with this concern while still holding therapeutic- and diagnostic-process claims such as the ones featured in this case and in *Lab. Corp.* patent-eligible under §101. Section 101 may appear to be unduly embracive, but that is only when read in a vacuum. By its own terms, §101 is only the first, not the final, hurdle a claim must clear before it can be patented.

Patentability ultimately turns on meeting "the conditions and requirements of" the rest of the Patent Act. 35 U.S.C. §101. Those "conditions and requirements" are

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[5] A central focus of Justice Stevens's concurring opinion in *Bilski* is the threshold question of whether a *business* method properly qualifies as a "process" within the meaning of §101. That unique issue is not raised by the claims at issue in *Prometheus* and *Lab. Corp.*, since they relate to therapeutic and diagnostic processes, which are undeniably useful and technological arts.

principally codified in §§102, 103, and 112 of the Patent Act. For example, §§102 and 103 preclude claims from covering subject matter that is anticipated by or obvious in view of the art. See, *e.g.*, *King Pharms., Inc.* v. *Eon Labs, Inc.*, 616 F.3d 1267, 1279 (Fed. Cir. 2010) (a claim to a method of treating musculoskeletal diseases by informing patients of the benefits of taking metaxalone with food was anticipated; the "informing limitation" confers no novelty on the claim since it does not change how metaxalone was administered with food in the prior art); *Schering Corp.* v. *Geneva Pharms., Inc.*, 339 F.3d 1373, 1382 (Fed. Cir. 2003) (method of treating hay-fever with a metabolite of loratadine was inherently anticipated because loratadine, a prior-art therapy, inherently converts to the metabolite upon ingestion); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1345, 1352 (Fed. Cir. 2002) (claims to growing sprouts to reduce the level of carcinogens and, in turn, the risk of developing cancer in animals that consume them were anticipated; the carcinogen-lowering potential of sprouts are "inherent properties * * * put there by nature" such that the patentee had "not claimed anything that is new"); *In re O'Farrell*, 853 F.2d 894, 904 (Fed. Cir. 1988) (producing the claimed genus of proteins would have been obvious in view of the prior art).

Section 102 provides an even further level of protection against claims that, unlike those at issue in this appeal and *Lab. Corp.*, are directed purely to physiological laws of nature because such laws are inherently in the prior art and hence anticipate such claims. See *EMI Group N. Am., Inc.* v. *Cypress Semiconductor Corp.*, 268 F.3d 1342, 1351 (Fed. Cir. 2001) (citing *Funk Bros. Seed*, 333 U.S. at 130).[6]

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[6] See also *KSR Int'l Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007) (expanding the circumstances under which claims can be deemed obvious);

Section 112, moreover, ensures that claims are properly supported by a specification describing their subject matter in a sufficiently clear and detailed fashion that they are deemed to be within the possession of the inventor and are "enabled," *i.e.*, can be made and used. See, *e.g.*, *O'Reilly* v. *Morse*, 56 U.S. (15 How.) 62, 119-120 (1853) (patent specification's description did not adequately support claims generically directed to using electromagnetism to print characters at a distance); *In re Fisher*, 421 F.3d 1365, 1367 (Fed. Cir. 2005) (claims to purified nucleic acid sequences that encode proteins and protein fragments in maize plants were not enabled, because "the claimed invention lacks a specific and substantial utility and * * * the * * * application does not [teach] one of ordinary skill in the art to use the invention"); *Regents of the Univ. of Cal.* v. *Eli Lilly & Co.*, 119 F.3d 1559, 1567 (Fed. Cir. 1997) (disclosure of the genetic sequence for rat insulin gene did not entitle the patentee to generically claim mammalian or vertebrate insulin genes or the human insulin gene).

Hence, to the extent a claim like the ones featured in *Prometheus* or *Lab. Corp.* raises concerns that a natural phenomenon itself is being wholly preempted because terms like "determining," "measuring," "assaying," etc., seemingly signify nothing more than mere "data-gathering," it should not be struck down under §101. Rather, the appropriate section under which to test the patentability of such a claim is §112, to ensure that there is sufficient written descriptive and enabling support in the specification to justify the breadth of terminology

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Bonito Boats, Inc. v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 156 (1989) ("Both the novelty and the nonobviousness requirements of federal patent law are grounded in the notion that concepts within the public grasp, or those so obvious that they readily could be, are the tools of creation available to all.")

used to claim the step of detecting the presence or amount of the relevant biomarker.

As the foregoing discussion shows, the Patent Act strikes a balance that renders frequent recourse to §101 unwarranted. Indeed, the Federal Circuit recently acknowledged that §101 is intended to function as a "coarse eligibility filter," with finer screening to come through the more restrictive conditions imposed under §§102, 103, and 112 of the Patent Act, which serve as the "final arbiter[s]" of whether a claim is patent-worthy. *Classen Immunotherapies, Inc.* v. *Biogen IDEC*, Nos. 2006-1634, 2006-1649, __ F.3d __, 2011 WL 3835409, at *8-10 (Fed. Cir. Aug. 31, 2011). See also *King Pharms.*, 616 F.3d at 1278 (noting that §102, not §101, was the appropriate vehicle for invalidating the medical treatment claims under review); cf. *Bilski*, 130 S. Ct. at 3235-3236 (Stevens, J., concurring in judgment) (recognizing that issues regarding a claim's novelty and breadth are properly dealt with under §§102 and 112 of the Patent Act, not §101).

The near total-reliance on §101 to invalidate the claims-at-issue by petitioner in this case, and the dissent in *Lab. Corp.*, would disrupt the relative and cooperative functions of §§101-103 and 112 in filtering out the unpatentable. Indeed, petitioner conflates the roles these distinct sections of the Patent Act are to play as filters by repeatedly injecting into the discussion questions as to the novelty, obviousness, and breadth of the claims-at-issue. Rather than couching these comments under the guise of §101, it would be more appropriate and analytically rigorous to acknowledge them as raising issues under §§102, 103, and 112 and, in turn, to address them under those sections.

That the Patent Act assigns different policing functions to different statutory provisions to cooperatively achieve the right result is hardly unique to patent law. Federal Rule of Civil Procedure 12(b), for example, pro-

vides a coarse screen in civil litigation; it requires dismissal when a complaint facially fails to state a claim or is brought before a court lacking jurisdiction. But asking Rule 12(b) to distinguish ultimately meritorious cases from those which ultimately will fail on the merits is asking too much. That function belongs to other provisions, such as the summary-judgment standards of Rule 56.

Complaining that §101 does not screen out all invalid patent claims makes no more sense than attacking Rule 12(b) for allowing cases that ultimately will fail on the merits to proceed. The question, in both contexts, is whether the system as a whole is capable of proper filtering. Nothing suggests that the Patent Act, as whole, performs that function inadequately. Unsurprisingly, when the Patent Act requires recalibration, Congress has responded—but not by revising §101. That bedrock provision has remained unchanged since 1952, when it was codified at its present location within Title 35. Indeed, even with the recent enactment of the Leahy-Smith America Invents Act of 2011, Congress adjusted the finer filters of §§102, 103, and 112, but not the coarse filter of §101.[7]

Section 101, in short, is a gatekeeper analogous to Rule 12. If the therapeutic- and diagnostic-process claims respectively at issue in this case and in *Lab. Corp.* truly were nothing more than an attempt to patent a "natural phenomenon," §101 would bar it. See *Lab. Corp.*, 548 U.S. at 137-138 (Breyer, J., dissenting). But as the Federal Circuit properly recognized, the therapeutic-process claims at issue here are applications which comfortably fall within the scope of §101—and indeed satisfy the narrow machine-or-transformation test by implicat-

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[7] See Pub. L. No. 112-29, §§3(b)(1) (amending 35 U.S.C. §102); 3(c) (amending 35 U.S.C. §103); and 4(c) (amending 35 U.S.C. §112), 125 Stat. 284, 285-287, 296.

ing transformative events. Pet. App. 14a-15a. As argued below in Part B, *infra*, the diagnostic-process claim at issue in *Lab. Corp.* similarly qualifies as an application of a law of nature that necessarily implicates transformative events.

B. Diagnostic processes like those at issue in *Lab. Corp.* are patent-eligible under §101 because they are applications of "laws of nature"

Viewing diagnostic-process claims like those at issue in *Lab. Corp.* as merely claiming laws of nature, as suggested by the *Lab. Corp.* dissent, is analytically flawed. That view overlooks expressly-recited claim steps and, as result, distorts the nature and import of such process claims. Such medically important subject matter is properly protected under §101 and should not be excluded from protection as an improper preemption of natural laws.

1. *The ability to detect or measure biomarkers makes personalized medicine possible*

Advancements in human genetic research have exploded in the 31 years since this Court considered the scope of patent-eligibility for biological subject matter under §101 in *Chakrabarty*. The Human Genome Project—the first complete sequencing of the entire human genome—is perhaps the most prominent example; it has captured the public's imagination in showing how far science has moved. By providing researchers with a detailed map of the genes on all 23 human chromosomes, the Project has accelerated the identification of relationships between specific genes and diseases. Products encoded by genes sequenced under the Project have complex interrelationships; teasing out those relationships, and identifying malfunctions in these gene products, particularly those that cause disease, have only just begun to produce improved medical treatments.

Finding those relationships holds far more than academic interest, because they provide unprecedented tools to detect, treat, and prevent disease. Indeed, the identification of those relationships is beginning to allow our healthcare system to *apply* them. Moving from identification to application shifts the paradigm from one of reaction to one of prevention—and one in which solutions, whether reactive or preventive, are tailored to the *individual's* unique biological makeup. Genetic tests have the potential to flag disease predisposition long before any symptoms occur, when steps can be taken to delay or even prevent what otherwise would be inevitable. That shift to prevention is widely recognized as having the potential to result in unprecedented gains in patient outcome and cost containment. See generally Allen et al., The New Science of Personalized Medicine (PricewaterhouseCoopers), Oct. 2009, at 3, 8, 26 (hereinafter "Allen").[8]

The promise genetic testing holds in shifting the practice of medicine to early-detection and disease prevention and management is already being realized. Indeed, the field is growing so fast that the National Center for Biotechnology Information, a branch of the NIH, has created an on-line virtual reference guide that documents how genetic testing is being used in the diagnosis, management, and counseling of patients and families with specific inherited conditions. See National Center for Biotechnology Information, GeneReviews (searchable database of entries).[9] The number of diseases for which genetic testing is available grew from just over 100 to 1,800 between 1993 and 2009. See Rugnetta et al., Genetic Non-Discrimination (Center for American Pro-

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[8] http://www.pwc.com/us/en/healthcare/publications/personalized-medicine.jhtml

[9] http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=GeneTests

gress), April 2008, at 2.[10] Among the tests currently available are ones that detect some of the most debilitating and life-threatening diseases afflicting our nation, including colon, endometrial, ovarian, and breast cancer; glandular disorders, such as cystic fibrosis; blood disorders, such as sickle cell anemia; and metabolic disorders, such as iron overload disease. See, *e.g.*, Disease Prevention and Genetic Testing—Can You Benefit?, Healthy Living (Johns Hopkins Health Alerts), Feb. 7, 2006;[11] Genetic Testing: What It Means For Your Health (NIH Pub. No. 07-6283), Aug. 2007, at 5.[12]

Recent advances in the biological sciences have also identified relationships between biomarkers and diseases that not only indicate an individual's predisposition for a particular disease, but also how a patient may respond to particular treatments for that disease. In the area of cancer treatment alone, numerous FDA-approved diagnostic tests are now available that are recommended for: (a) identifying sub-populations that are predisposed to favorably respond to particular anti-cancer therapies; and (b) monitoring patients' responses to those therapies. Such therapies include Herceptin (breast cancer),[13] Xalkori (lung cancer),[14] Erbitux (colorectal cancer),[15]

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[10] http://www.americanprogress.org/issues/2008/04/pdf/gina_report.pdf

[11] http://www.johnshopkinshealthalerts.com/reports/healthy_living/133-1.html

[12] http://www.genome.gov/Pages/Health/PatientsPublicInfo/GeneticTestingWhatItMeansForYourHealth.pdf

[13] See FDA Approves Use of PathVysion(R) Breast Cancer Test to Select Appropriate Candidates for Herceptin(R) Therapy, PR Newswire, Jan. 10, 2011, at http://www.prnewswire.com/news-releases/fda-approves-use-of-pathvysionr-breast-cancer-test-to-select-appropriate-candidates-for-herceptinr-therapy-75389347.html

[14] See FDA, FDA, Vysis ALK Break Apart FISH Probe Kit, with the Vysis Paraffin Pretreatment IV and Post Hybridization Wash Buffer Kit, ProbeChek ALK Negative Control Slides, and Probe-

Gleevec/Glivec (gastrointestinal cancer),[16] and Zelboraf (skin cancer).[17]

The identification of biomarkers that help predict the efficacy of particular therapies permits physicians to tailor a treatment regimen for a particular patient. Such tailoring, in turn, lowers healthcare costs. Lower healthcare costs benefit not only individual patients and public and private insurance companies, but also the federal and state governments that now bear substantial and increasing healthcare funding obligations. Personalized medicine achieves significant efficiencies—and dramatic improvements in results and quality of life—by identifying which therapeutics will work for a particular patient, and which might be less effective. Crucially, this is done without physicians having to engage, as they have traditionally, in the expensive, time-consuming, often empirical, and sometimes painful or tragic process of racing against the clock to determine whether a patient will respond favorably to a therapy. Indeed, the current Direc-

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Chek ALK Positive Control Slides—P110012 (webpage containing device information and link to approval letter), at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm270832.htm

[15] See FDA, DakoCytomation EGFR pharmDx™—P03044 (webpage containing device information and link to approval letter), at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm081222.htm

[16] See FDA, Ventana Medical Systems' PATHWAY Anti c-KIT (9.7) Primary Antibody (webpage containing device information and link to approval letter), at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm080911.htm

[17] See FDA, Cobas® 4800 BRAF V600 Mutation Test—P110020 (webpage containing device information and link to approval letter), at http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm268836.htm

tor of the NIH noted that "personalized medicine remains one of the most compelling opportunities we have to improve the odds of staying healthy." Collins, Personalized Medicine, Boston Globe, July 17, 2005, at E12.[18]

Novartis and many other healthcare companies are expending hundreds of millions of dollars to identify new biomarkers and apply their detection to new diagnostic and therapeutic methods. See Allen, *supra*, at 3, 17; Pollack, Drug Companies Pursue Personalized Medicine Approach, N.Y. Times, Nov. 16, 2010 ("Prescriptions" blog post).[19] Although driven by the desire to improve healthcare, the prospect of patent protection also provides an important incentive to expend—and the necessary protection to fund—the time and effort necessary to make biomedical discoveries and translate them into new medical procedures that help patients. The days of administering a drug to all patients sharing a particular disease—despite the reality that, for some, it may not do any good—are, fortunately, waning. Instead, healthcare companies are identifying the patient sub-populations most likely to benefit from any one particular therapy. Thus, it is of paramount importance that appropriate consideration be given to the patentability of the process claims at the heart of personalized medicine.

It is all too easy to dismiss the relationships being identified in this new era of personalized medicine as discoveries of the laws of nature. After all, they implicate correlations between (1) biomarkers that are actively measured and (2) a patient's predisposition to having a disease, a patient's likely response to a particular drug, or a patient's need for the dosage of a particular drug to

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[18] http://www.boston.com/news/globe/editorial_opinion/oped/articles/2005/07/17/personalized_medicine/

[19] http://prescriptions.blogs.nytimes.com/2010/11/16/drug-companies-pursue-personalized-medicine-approach

be adjusted. But the discovery of those relationships and their utility in treating diseases can represent a critical advance in the important art of making the unhealthy healthy, or providing the individual who is prone to disease with immunity to its effects. Where a new and useful process for identifying those who are at risk of disease or most likely to benefit from a particular treatment is discovered, it represents a true advance in the art of medicine and technology. When a process claim clearly calls for the detection or measurement of a relevant biomarker, such claim language should suffice for the claim to be patent-eligible under §101. The fact that it does not further explicitly refer in words to a particular machine or transformation (as with the claim at issue in *Lab. Corp.*) or spell out a subsequent treatment step (as with the claims at issue in this case) should not prejudice its patent-eligibility.

2. *The ability to patent diagnostic processes provides critical incentives for life-sciences companies to advance medicine and invest in local economies*

The incentives afforded by the patent system, which spur on medical advancements, would be imperiled were the Court to adopt the approach urged by petitioners here or by the dissent in *Lab. Corp.* Without access to patent protection, and the economic benefits such protection affords, companies like Novartis would be significantly discouraged from making the investments necessary to bring about medical advancements such as those discussed above.

Indeed, it is that very access to patent protection that helped spur Novartis Vaccines & Diagnostics, Inc. (NVD) (previously Chiron Corporation) to invest in the research and development of diagnostic assays that currently protect our country's donor blood supply against HCV, HIV, and Hepatitis B infections. Similarly, the same access to

patent protection today provides the incentive for NVD to pursue the research and development of other diagnostic tests, including those that will safely and accurately identify hereditary diseases and help preserve the integrity of banked donor bone marrow used in transplant procedures.

But the economic importance of being able to protect a company's medical innovations reaches beyond the research and development activities conducted on its campus. The protections afforded by patent-eligibility also fuel the very economies where companies have or intend to have a presence. Novartis's decision to expand its operations in Cambridge, Massachusetts, is a case in point. Despite the present economic crises, the company expects to spend $600 million to bolster its research operations and strengthen partnerships with local universities and biotechnology start-ups. See Weisman, At Novartis, A Winning Formula, Boston Globe, Jan. 4, 2011, at A1.[20] It also estimates hiring an additional 200-300 employees over the next five years, which would bring the total Novartis workforce in Cambridge alone to about 2,300. Such investments would be jeopardized without access to patent protection, and a potential for return on that investment. And yet it is these very types of investments that will be critical not only to preserving the health of Americans, but also to sustaining our economy.

3. *The claim at issue in* Lab. Corp. *is patent-eligible under § 101*

The inventions at issue here and in *Lab. Corp.* are not only of vital importance, but also plainly fit within traditional criteria of patent-eligibility. Understanding why the approach taken by the *Lab. Corp.* dissent would have been the wrong one to resolve the § 101 issue raised there

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[20] http://articles.boston.com/2011-01-04/business/29348116_1_novartis-research-drug-discovery-big-pharma

is important. This is because it underscores why that approach is the wrong one generally, and should not govern the Court's resolution of this case.

The controversy in *Lab. Corp.* involved a method for detecting certain B vitamin (cobalamin or folate) deficiencies. See *Metabolite Labs., Inc.* v. *Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1358-1359 (Fed. Cir. 2004). Deficiencies in cobalamin and folate are medically significant. If left untreated, such deficiencies can lead to serious complications including cardiovascular, neurologic, and psychiatric pathologies, such as stroke, peripheral neuropathy, and depression. See, *e.g.*, Oh & Brown, Vitamin B12 Deficiency, 67 Am. Fam. Physician 979, 979 (2003). Claim 13 of U.S. Patent No. 4,940,648, the only claim at issue in *Lab. Corp.*, reads as follows:

> 13. A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:
>
> assaying a body fluid for an elevated level of total homocysteine; and
>
> correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.

See 370 F.3d at 1358-1359. The law of nature relied upon in the claimed method is the fact that cobalamin and folate are used by the body as co-factors for enzymatic activity. Much as an automobile engine cannot convert gasoline into motive power in the absence of spark plugs, the enzyme that the body employs to convert homocysteine into cysteine cannot effectively accomplish that conversion in the absence of its co-factors cobalamin and folate. Thus, an increase in homocysteine and a decrease in cysteine, both of which would occur if the enzyme were not functioning properly, may be indicative of a deficiency in one or both co-factors. Claim 13 therefore

represents a particular application of the discovery that homocysteine is converted to cysteine by an enzyme requiring cobalamin or folate as a co-factor for optimal activity. Specifically, the claim is directed to measuring increased levels of homocysteine (which occur because it is not being enzymatically converted to cysteine) as a biomarker for a cobalamin or folate deficiency.

a. *The significance of claim 13's "assaying step" was lost because of how the issues were framed in* Lab. Corp.

The concerns raised by Justice Breyer in his dissent in *Lab. Corp.* are significant and deserve a full and robust debate. But the debate in *Lab. Corp.* was distorted by the way in which that case had been litigated, and the issues framed in the lower courts. Under controlling jurisprudence, patent-infringement liability attaches to a method claim when a single party can be held accountable for practicing all steps of the claim. See *Muniauction, Inc.* v. *Thomson Corp.*, 532 F.3d 1318, 1328-1330 (Fed. Cir. 2008) (a method claim is infringed only when a single party can be found to have performed every step of the claim, or where a party can be held vicariously liable for others practicing those steps).[21] In *Lab. Corp.*, the parties did not dispute before the Federal Circuit whether the accused direct infringers performed one of the critical steps, which was the assaying step. See *Metabolite Labs.*, 370 F.3d at 1364 n.1. Instead, the focus of the parties' arguments was solely on the district court's interpretation of the correlating step of the claim and whether, as a result of that construction, the accused di-

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[21] The Federal Circuit has recently ordered an *en banc* rehearing to further address questions of when the activities of multiple parties can lead to a finding of direct patent infringement. See *McKesson Techs. Inc.* v. *Epic Sys. Corp.*, No. 2010-1291, 2011 WL 2173401 (Fed. Cir. May 26, 2011) (*per curiam*) (order).

rect infringers could be said to have performed it. Because the assaying step was not in dispute, at least with respect to infringement, it faded from view.

The exclusive focus of the infringement inquiry on the correlating step all but ensured that the import of the assaying step would be conceptually disregarded as merely "gather[ing] data" in the context of the dissent's §101 analysis. See *Lab. Corp.*, 548 U.S. at 137 (Breyer, J., dissenting). Without the benefit of a fully developed record regarding the meaning and import of the assaying step, the *Lab. Corp.* dissent naturally focused its analysis of the claim on only the correlating step. In turn, therefore, it viewed the claim as impermissibly directed to nothing more than a law of nature—that elevated homocysteine levels indicate a deficiency in cobalamin or folate—in violation of §101.[22]

The assaying step, however, is an integral limitation of the claim that cannot be disregarded when analyzing the claim's compliance with §101. Indeed, were the correct analysis applied, it would have been clear that the claim does not attempt to monopolize a law of nature. It is a general principle of patent law that "claims must be con-

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[22] Given the underlying importance of claim construction to the §101 analysis, any reversal of the judgment in this case will invariably be driven by how the Court construes the scope of the claims-at-issue as they are worded. The likely influence of such idiosyncratic features on a disfavorable ruling strongly cautions that this case is not the proper vehicle for broadly holding that all therapeutic- or diagnostic-process claims, no matter how worded and construed, are necessarily patent-ineligible under §101. Accordingly, even if this Court were to reverse the judgment below, it should reserve for another day the patent-eligibility of other claims directed to therapeutic- and diagnostic-processes. That would ensure that the Court's holding is limited to the facts and issues before it and, in turn, ensure that the patent-eligibility of a differently-worded therapeutic- or diagnostic-process is only reached after a full record is developed in an appropriate case squarely raising that claim's compliance with §101.

sidered as a whole." *Diehr*, 450 U.S. at 176, 188; see also *Aro Mfg. Co.* v. *Convertible Top Replacement Co.*, 365 U.S. 336, 345 (1961) (applying this principle to analyzing infringement); *Para-Ordnance Mfg., Inc.* v. *SGS Importers Int'l, Inc.*, 73 F.3d 1085, 1088 (Fed. Cir. 1995) (applying the principle to a determination of obviousness).

The assaying step of claim 13 serves a critical function. Beyond providing a measurement needed to make the correlation that the second step of the claim requires, the assaying step enables a diagnosis to be made with respect to a particular patient and, in turn, the patient to be put on an appropriate therapy. That is no trivial matter. By according the assaying step its proper meaning, claim 13, as a whole, is no longer directed simply to the law of nature *itself*, but to a practical *application* of that law.

b. When properly construed, claim 13 does not preempt a law of nature

Because claim 13 is directed to an application of a law of nature, it does not preempt "'basic tools of scientific and technological work,'" *Lab. Corp.*, 548 U.S. at 127 (Breyer, J., dissenting) (quoting *Gottschalk*, 409 U.S. at 67), that should be free for anyone's use. Significantly, the claim does not encroach on the practice of medicine as envisioned in the dissent. For example, the claim does not prevent doctors from drawing conclusions based on test results they are not accountable for generating. Similarly, the claim presents no bar to doctors mentally considering or applying the correlation when it is not tied to assaying a sample. Nor does the claim cover the population of people whose bodies inherently manifest the correlation because they are deficient in cobalamin or folate. Rather, the claim is limited to only those situations where a single actor, based on his own actions or those of others for which he is legally accountable, can be held liable for both: (a) assaying the amount of homocys-

teine present in a body fluid; and (b) correlating an elevated amount with a cobalamin or folate deficiency.

c. Claim 13 requires human intervention and implicates transformative events

Other considerations further support the patent-eligibility of claim 13. For example, the assaying step requires considerable human intervention; a doctor cannot detect a deficiency in cobalamin or folate through simple observation of a patient. Such a diagnosis can only be reached following testing of a sample. Hence, claim 13 falls comfortably within *Diehr*'s recognition of the Patent Act's embracement of "man-made" creations. *Diehr*, 450 U.S. at 182.

The patentee in *Lab. Corp.* was also correct in arguing to this Court that the assaying techniques necessary to measure cobalamin and folate levels (like the techniques used to determine metabolite levels in respondent's claimed processes) do invariably implicate transformations of one form or another. Hence, the claim-at-issue did not need to recite a particular assaying means, as the dissent suggests, see 548 U.S. at 136 (Breyer, J., dissenting), for the patentee to avail itself of such an argument; the claim language should have sufficed. Moreover, there is nothing otherwise inappropriate about using a term such as "assaying" (or "detecting" or "measuring") in the first step of a diagnostic-process claim, so long as: (a) such a term is properly supported by the specification under §112, see, *e.g.*, *In re Swinehart*, 439 F.2d 210, 213 (C.C.P.A. 1971); *In re Grimme*, 274 F.2d 949, 952 (C.C.P.A. 1960); and (b) the claim, as a whole, does not read on the prior art under §§102 and 103.

d. Diagnostic-process claims worded similarly to claim 13 are likewise patent-eligible and do not unfairly restrain doctors' ability to diagnose or counsel

The points made above are equally applicable to virtually any comparably-worded diagnostic-process claim relating to personalized medicine. At a minimum, such claims involve an assay or detection step, such as a genetic test to determine the presence or absence of a particular DNA sequence. The assay or detection step enables a correlation to be drawn between the presence or absence of that DNA sequence and a predisposition for either developing a disease or being receptive to a particular therapy. In such contexts, the act of assaying or detecting the DNA sequence, or some other biomarker, is a significant corporeal intervention that invariably implicates transformative events.

Indeed, in many instances the DNA sequence actually being probed for is present in a synthetically-generated DNA fragment that corresponds to a portion of a naturally-occurring gene found in a chromosome. The Federal Circuit has recently acknowledged that such synthetic DNA molecules are not products of nature and, hence, are patent-eligible "compositions of matter" under §101. That holding stems from an appreciation that such molecules "are not the same molecules as DNA as it exists in the body; human intervention in cleaving or synthesizing a portion of a native chromosomal DNA imparts on that isolated DNA a distinctive chemical identity from that possessed by native DNA." See *Ass'n. for Molecular Pathology* v. *U.S.P.T.O.*, 653 F.3d 1329, 1352 (Fed. Cir. 2011) (hereinafter "*Myriad*"). The patent-eligibility of such subject matter should, in turn, impart patent-eligibility on diagnostic process-claims that are predicated on generating such DNA molecules and correlating specific sequences within them to a predisposition

for either developing a disease or receptiveness to a particular therapy. Both the Federal Circuit and the *Lab. Corp.* dissent appear to agree that a therapeutic- or diagnostic-process claim reciting a natural phenomenon can be patent-eligible provided it contains other limitations that impart patentability to the claim as a whole. See *Lab. Corp.*, 548 U.S. at 136 (Breyer, J., dissenting); *Myriad*, *supra*, at 1356-1357.[23]

Moreover, regardless of what form a biomarker may take, the step of detecting that biomarker enables the law of nature to be applied to facilitate a diagnosis or treatment. Such applications of the law of nature take the claim out of the realm of monopolizing the law of nature itself. Again, when not accountable for performing an assaying or detection step, doctors do not infringe when they use the results of such a step to counsel a patient. By embodying so much more than mere naturally-occurring correlations, diagnostic claims relating to personalized medicine fall well within the scope of §101, as defined by this Court's precedent.

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[23] Some of the claims at issue in *Myriad* were directed to methods of "comparing" and "analyzing" nucleotide sequences to determine whether a patient carried biomarkers for certain cancers. The claims, however, were viewed as not requiring the generation of synthetic DNA molecules or any manipulation of a patient sample or a patient's DNA, each of which would have necessarily implicated transformative events. Because the claims were interpreted broadly enough to read on a mere analysis or comparison of nucleotides found at particular positions within a sequence, they were deemed to impermissibly claim an intellectual abstraction in violation of §101. Notably, the claims at issue in *Myriad* never benefitted from a full-blown *Markman* analysis as to their proper construction. See *Myriad*, 653 F.3d at 1355-1357.

4. *The* Lab. Corp. *dissent's analysis improperly threatens diagnostic-process claims*

The *Lab. Corp.* dissent's unreasonably rigid analysis jeopardizes the patent-eligibility of diagnostic-process claims. As shown above, diagnostic-process claims are based on discoveries of previously-unknown relationships, and, in some instances, discoveries of novel and non-obvious biomarkers, without which the benefits they unlock would remain hidden. Additionally, they are indisputably "useful." Personalized medicine can be the difference between life and death. It directly enhances the quality of, or even sustains the very existence of, human life. It is hard to imagine a more "useful" invention than a process applying newly discovered natural relationships to that end.

The diagnostic-process claims at the heart of personalized medicine are the result of the same kind of intellectual exertion and have the same utility as machine-age processes, even though they are couched in the language of molecular biology rather than that of mechanics and electronics. Factual and policy considerations in the twenty-first century show the wisdom of this Court's description of §101 as a "dynamic provision designed to encompass new and unforeseen inventions." *J.E.M. Ag Supply*, 534 U.S. at 135 (2001); see also *Bilski*, 130 S. Ct. at 3239 (Stevens, J., concurring in judgment). Whereas the Federal Circuit takes an approach consistent with §101's dynamics in the instant appeal, the *Lab. Corp.* dissent takes the opposite approach when evaluating the patent-eligibility of the diagnostic-process claim at issue there. It trivializes the diagnostic process claimed as essentially directed to nothing more than a law of nature coupled to mere data-gathering or post-solution activity, effectively and improperly reading out an express limitation of the claim.

* * *

The analysis suggested in the *Lab. Corp.* dissent has the potential to deny patent-eligibility to diagnostic-process claims that are no less deserving of that protection than any other new and useful discovery. It would do so, moreover, by distorting the reach of §101 and by refusing to acknowledge the full content of those claims. Nothing in the text or history of §101 suggests that patent-eligibility ought not extend to the valuable fruits of the exacting labor that must be invested to develop such important new medical advances. Nor is there any basis for this Court engrafting such an exclusion into the statute itself.

CONCLUSION

This Court's precedents regarding patent-eligibility under 35 U.S.C. §101 have served the country well in advancing the useful arts and, if reaffirmed, will continue to do so. The Court should therefore maintain its broad interpretation of §101 and affirm the Federal Circuit's judgment that the claims at issue in this case are patent-eligible under §101. Whether in the context of a therapeutic process or a diagnostic process, where the detection or measurement of a biomarker and its medical utility are applied in furtherance of patient care, a claim to such processes merits the same protections afforded by the law to other new and useful inventions.

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AMICUS CURIAE BRIEF

No. 10-1150

IN THE
Supreme Court of the United States

MAYO COLLABORATIVE SERVICES, DBA MAYO MEDICAL LABORATORIES, ET AL.,
Petitioners,

v.

PROMETHEUS LABORATORIES INC.,
Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF *AMICUS CURIAE*

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is a voluntary, nonprofit association that represents the country's leading research-based pharmaceutical and biotechnology companies.[1] In the past decade, PhRMA's members have invested more than $406 billion to discover and develop new medicines and new uses for existing medicines. *See* PhRMA, PHARMACEUTICAL INDUSTRY PROFILE 2011 at 42 (2011). In 2010 alone, the pharmaceutical industry invested a record $67.4 billion in such research and development.

The results of this research save lives. *See generally* Frank R. Lichtenberg, *The Impact of New Drug Launches on Longevity: Evidence from Longitudinal, Disease-Level Data from 52 Countries, 1982-2001*, 5 Int'l J. of Health Care Fin. & Econ. 47, 71 (2005). Today, "the most important advances in treatment" often come from new uses for existing pharmaceuticals – products "whose properties were not completely understood until intensive research after the drug was introduced." John Calfee, *The Golden Age of Medical Innovation*, The American (Mar./Apr. 2007), *available at* http://www.american.com/archive/2007/march-april-magazine-contents/the-golden-age-of-medical-innovation

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[1] Pursuant to Supreme Court Rule 37.6, *amicus* states that no counsel for any party authored this brief in whole or in part, nor did any party, counsel for a party, or person other than *amicus*, its non-party members, or their counsel make a monetary contribution intending to fund this brief's preparation or submission. All parties have consented to this filing.

[hereinafter "*Golden Age*"]. Researchers are also making significant advances in "personalized" medicine, which tailors treatment to a particular patient's genetic or other biological characteristics. Life-saving treatments in these two areas include, for example, the use of AZT to treat HIV and the use of Herceptin to treat a particular group of breast cancer patients.

The Court's decision in this case will potentially have a significant impact on PhRMA's members.[2] A ruling limiting the availability of patents for medical processes under 35 U.S.C. § 101 could dramatically diminish the incentives for investment in innovation. The average cost of bringing a pharmaceutical to market is over a billion dollars. Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 Managerial & Decision Econ. 469, 477 (2007). The costs of developing processes for new uses for existing drugs and processes for personalized medicine are similarly substantial. *See, e.g.*, Maya Said et al., *Continued Development of Approved Biological Drugs: A Quantitative Study of Additional Indications Approved Postlaunch in the United States* 6 (Boston Consulting Group, White Paper, Dec. 2007), *available at* http://www.bcgsea.com/documents/file15138.pdf. In the absence of the incentives provided by patent protection for novel processes, promising research for new methods of diagnosis and treatment likely will not occur.

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[2] A list of PhRMA members can be found at http://www.phrma.org/about/member-companies.

SUMMARY OF ARGUMENT

This Court's decisions make clear that a broad range of subject matter is eligible for patent protection under 35 U.S.C. § 101. They also make clear that the "law of nature" exception to § 101 should be interpreted narrowly. Under these decisions, medical-process patents involving pharmaceuticals – which are the products of human ingenuity, and cannot be found in nature – necessarily fall within the scope of § 101.

Congress has also clearly expressed its intent to protect medical-process patents involving pharmaceuticals. It has, for example, provided for term extensions for patents covering a "method of using" a drug product, 35 U.S.C. § 156(a), and has decided not to enact legislation that would have restricted the patentability of medical processes. Moreover, Congress has balanced the interests of physicians and inventors by immunizing physicians when they infringe certain method patents, but not when they infringe patents for new uses of pharmaceuticals.

Under this regime, medical innovation has thrived. Patents for medical processes, including those involving pharmaceuticals, have been issued and upheld for more than a hundred years. At present, tremendous and life-saving advances are being made with respect to various kinds of medical processes, including new uses for existing pharmaceuticals and processes for "personalized" medicine. These advances, which entail extraordinary risk and expense on the part of the

pharmaceutical and biotechnology industries, likely would not take place without the certainty and stability provided by the promise of patent protection.

Petitioners seek to change the law so as to destabilize this regime, and undercut the incentives for innovation, in at least three ways – all of which should be rejected. First, this Court should rebuff Petitioners' suggestion to import an obviousness inquiry into the test for patentability under § 101. Second, the Court should decline to break apart a medical-process claim into its discrete steps for purposes of ascertaining whether a natural law is at play. Finally, the Court should make clear that assessment of whether a patent has an undesirably broad preemptive effect is a policy judgment best left to Congress, and does not control the determination of whether the patent's subject matter is eligible for protection under § 101.

ARGUMENT

I. Under This Court's Precedents, Medical-Process Patents Involving Pharmaceuticals Are Patentable Under Section 101

Section 101 provides that any "new and useful process" or "any new and useful improvement thereof" is entitled to patent protection, making no exception for any particular type of process. 35 U.S.C. § 101. Congress wrote § 101 with intentional breadth. The wide scope of patentable subject matter, beginning with the 1793 Patent Act and extending through each subsequent re-codification, reflects Jefferson's view that "ingenuity should

receive a liberal encouragement." *Diamond v. Chakrabarty*, 447 U.S. 303, 308-09 (1980) (quoting 5 Writings of Thomas Jefferson 75-76 (H. Washington ed. 1871)); *see also Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010); *Diamond v. Diehr*, 450 U.S. 175, 182 (1981); PTO, *Interim Guidance for Determining Subject Matter Eligibility for Process Claims in View of Bilski v. Kappos*, 75 Fed. Reg. 43,922, 43,926 (July 27, 2010) (describing § 101 as "coarse filter").[3] It also gives the law sufficient flexibility to meet "the revelations of . . . onrushing technology." *Gottschalk v. Benson*, 409 U.S. 63, 71 (1972).

This Court has long identified "three specific exceptions to § 101's broad patent-eligibility principles: laws of nature, physical phenomena, and abstract ideas." *Bilski*, 130 S. Ct. at 3225. These exceptions "are not the kind of 'discoveries' that the statute was enacted to protect," *Parker v. Flook*, 437 U.S. 584, 593 (1978), because "they are the basic tools of scientific and technological work," *Gottschalk*, 409 U.S. at 67; *see also Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948), which must be available for building future inventions, *Bilski*, 130 S. Ct. at 3231.

But these exceptions must be applied "narrowly." *Bilski*, 130 S. Ct. at 3229. The "relevant distinction" is "between products of nature . . . and human-made invention." *Chakrabarty*, 447 U.S. at 313. Thus, it is not possible to patent "the heat of the sun,

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[3] The Patent Act of 1793 used the term "art," which Congress replaced with "process" when it enacted the current version of § 101 in 1952. *In re Bilski*, 545 F.3d 943, 951 n.4 (Fed. Cir. 2008), *aff'd*, 130 S. Ct. 3218 (2010).

electricity, or the qualities of metals," *Funk Bros.*, 333 U.S. at 130, or the "law that $E=mc^2$" or the "law of gravity," or "a new mineral discovered in the earth or a new plant found in the wild," *Chakrabarty*, 447 U.S. at 309. But when human ingenuity is applied to create a process that involves these natural laws or objects, § 101 is satisfied. *See, e.g.*, *Mackay Radio & Tel. Co. v. Radio Corp. of America*, 306 U.S. 86, 94 (1939).

This Court's recent decision in *Bilski v. Kappos*, 130 S. Ct. 3218 (2010), reaffirmed this longstanding approach. The Court emphasized that any limits on the scope of patentability under § 101 must "further the purposes of the Patent Act" and be consistent "with its text." *Id.* at 3231. And the Court rejected two "atextual" rules – that "business processes" are categorically unpatentable and that the "machine or transformation" test should be the "exclusive" means for determining whether a process satisfies § 101. *Id.* at 3229. At the same time, however, the Court described the machine-or-transformation test as "a useful and important clue, an investigative tool, for determining whether some claimed inventions are processes under § 101." *Id.* at 3227; *see also id.* at 3232 (Stevens, J., concurring) ("the entire Court agrees" that "the machine-or-transformation test is reliable in most cases"); *Cochrane v. Deener*, 94 U.S. 780, 788 (1877).

Patents involving pharmaceuticals – whether they cover a chemical substance or a process in which that substance is measured or employed – necessarily involve such a transformation, and fall within the scope of § 101. Pharmaceuticals are not

found materials like minerals or plants; they exist only as the result of human ingenuity. And the mixing of chemical substances, or a process for chemical transformation of a substance or object, is in the heartland of patent-eligible subject matter. *See, e.g.*, *Tilghman v. Proctor*, 102 U.S. 707, 728 (1881) ("The mixing of certain substances together, or the heating of a substance to a certain temperature, is a process."). That is true not only when the chemicals are mixed in a laboratory beaker but also when they are put into or measured in the human body. In this case, for example, the patent covers the administration of a man-made drug, which creates metabolites in the body that would not exist in the absence of that drug, as well as the determination of the resulting effects on the patient.[4] Pet.App.17a-18a (description of "effect on the body after metabolizing the artificially administered drugs" and transformation entailed in "extract[ing] the metabolites . . . and determin[ing] their concentration"); *see also* Gov't Br. 13-14. Although there are natural laws at work that help explain why the drug creates a particular metabolite at particular levels, none of this is purely the "handiwork of nature." *Chakrabarty*, 447 U.S. at 310.

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[4] The patents here claim "methods for optimizing efficacy and reducing toxicity of treatment regimes for . . . autoimmune diseases that utilize drugs" that create metabolites called 6-TG and 6-MMP. Pet.App.16a-18a. Some of the claims contain three steps: (1) "administering" a drug that creates the metabolites, (2) "determining" the resulting metabolite levels, and (3) warning of "'a need' to increase or decrease the level of drug." *Id.* at 3a. Others contain only steps 2 and 3. *Id.* at 18a.

II. Congress Has Balanced Competing Policy Considerations And Clearly Expressed Its Intent To Provide Patent Protection For Medical Processes Involving Pharmaceuticals

Congress has also made clear that medical processes are patentable, especially if they involve the administration of a pharmaceutical or a new use for a pharmaceutical. Any interpretation of § 101 that excludes medical processes involving pharmaceuticals would effectively write a number of provisions out of the U.S. Code, and would contravene other strong evidence of congressional intent.

As an initial matter, the statutory definition of "process" demonstrates that the mere fact that a process uses an existing compound does not remove it from the scope of patent protection. The statute defines the term "process" to mean "process, art or method" and states that it "includes a new use of a known process, machine, manufacture, composition of matter, or material." 35 U.S.C. § 100(b). Accordingly, the fact that the patent at issue in this case makes use of a pharmaceutical that was invented by others, *see* Pet.Br.37 n.7, or a process for adjusting dosage that was already known in the art, does not remove Respondents' claims from the scope of patentable subject matter under § 101. *See infra* pp. 28-30 (discussing separate role of obviousness in determining validity).

Congress has also more specifically addressed patents involving a method of using a pharmaceutical, in several different enactments.

First, the Hatch-Waxman Act, Pub. L. No. 98-417, 98 Stat. 1585, assumes that such methods are patentable. In that statute, Congress required parties applying for approval of a new drug to list certain related patents, including any patent "which claims a method of using such drug." 21 U.S.C. § 355(b)(1). Congress also required applicants to provide supplemental information when any new patents issue, including new patents on methods of use. *Id.* § 355(c)(2). And Congress provided (under some conditions) for term extensions for patents claiming not only a "method of manufacturing a [pharmaceutical] product" but also "a method of using a [pharmaceutical] product." 35 U.S.C. § 156(a); *see also id.* § 156(f). Plainly, Congress would not have enacted these provisions if it did not intend for these processes to be patentable or if it believed that a significant subset of pharmaceutical-related medical-process patents fell outside the scope of § 101. *Edelman v. Lynchburg Coll.*, 535 U.S. 106 (2002).

Second, in 1996, Congress *rejected* a proposal to preclude the issuance of a patent for any medical procedure that did not use a patentable product, and instead decided to exempt medical professionals from patent remedies *except* when they are violating patents for new uses of pharmaceuticals. This legislation arose in reaction to a controversy over a lawsuit by one physician against another for purportedly infringing a patent on a method of surgery – the first case of its type to go to trial. *See* Todd Martin, *Patentability of Methods of Medical Treatment: A Comparative Study*, 82 J. Pat. &

Trademark Off. Soc'y 381, 405 (2000); 142 Cong. Rec. 26,825-26 (1996) (statement of Sen. Frist). The bills initially introduced in the House and Senate would have either precluded the issuance of patents for medical procedures altogether unless the underlying product was itself patentable, H.R. 1127, 104th Cong. (1995), or redefined what would constitute infringement of patents for medical processes, including protecting medical professionals from any liability in that arena, S. 1334, 104th Cong. (1995). Neither bill attracted much support. *See* Richard P. Burgoon, Jr., *Silk Purses, Sows Ears and Other Nuances Regarding 35 U.S.C. § 287(c)*, 4 U. Balt. Intell. Prop. L.J. 69, 79-80 (1996).[5]

Instead, Congress took a nuanced approach that expressly recognized the importance of medical-process patents covering processes that employ pharmaceuticals. Congress decided to protect the interests of medical professionals to only a limited degree, shielding them when they are performing a medical activity unless they infringe certain specific kinds of biotechnology patents. Thus, the statute provides that "[w]ith respect to a medical practitioner's performance of a medical activity that constitutes an infringement . . . the [remedial] provisions . . . of this title shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity." 35

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[5] Congress had also previously considered and rejected similar legislation. H.R. 12,451, 57th Cong. (1902); H.R. 13,679, 58th Cong. (1904); William D. Noonan, *Patenting Medical and Surgical Procedures*, 77 J. Pat. & Trademark Off. Soc'y 651, 654 (1995).

U.S.C. § 287(c)(1). But it then *excludes* from the definition of "medical activity" – and thus from the scope of the immunity provision – the "practice of a patented use of a composition of matter" and "the practice of a process in violation of a biotechnology patent." *Id.* § 287(c)(2)(A); *see also id.* § 287(c)(2)(F).[6]

Thus, it is plain that Congress – having thoroughly considered the issue – wanted to protect *all* medical-process patents involving pharmaceuticals, including those that cover the relationship between the levels of a pharmaceutical in the body and a patient's health. The legislative history underscores that conclusion. According to the Conference Report, "'[u]ses of compositions of matter' include, without limitation, novel uses of drugs . . . and novel methods for providing genetic or other biological materials to a patient." H.R. Rep. No. 104-863, at 853 (1996). The report gives two examples of situations in which doctors would not be immunized: infringement of (1) "a claim that recites only the novel use of a drug for the treatment of diabetes that involves the administration of a drug at a particular time of day and/or at a specified dose and/or with a specified concomitant medicinal therapy," and (2) a claim for a method of transplant surgery that uses a novel anesthetic or a novel dosing schedule for that anesthetic. *Id.* at 853-54. Accordingly, even if a dosing schedule essentially embodies what Petitioners describe as a natural

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[6] Congress has similarly exempted researchers from liability for infringement under certain limited circumstances. 35 U.S.C. § 271(e)(1); *see also Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005); Roche Amicus Br. 25-27.

correlation, it remains patentable, and doctors remain subject to patent remedies if they infringe the patent.

In explaining this legislation, Senator Frist focused heavily on the need to preserve the incentives for innovation that have produced the kinds of medical advances described in Part III below. He discussed the need for innovators to recoup their investments and noted that prior versions of the legislation "could have impacted many worthwhile patents in biotechnology and pharmacology." 142 Cong. Rec. 26,825 (1996). In contrast, the legislation as it was ultimately enacted was not intended to "change patent law with respect to biotechnology, . . . drugs, or their methods of use," so as not to "discourage the important research being done in these areas of medicine." *Id.*

All of this makes clear that Congress has weighed the various policy considerations that Petitioners identify, *see, e.g.*, Pet.Br.48-58, and has decided that medical-process patents involving methods of using pharmaceuticals are entitled to protection even if they could conceivably affect the practice of medicine in some narrow circumstances. Because Congress has already determined that the benefits of pharmaceutical-related medical-process patents in spurring life-saving innovation outweigh any burdens that may be associated with those patents during their limited terms, Petitioners' concerns are wholly misplaced. *See Chakrabarty*, 447 U.S. at 317; *cf. Bilski*, 130 S. Ct. at 3228-29 (construing § 101 in light of statutory defense to infringement of business-method patents).

Congress's enactments also show that any interpretation of § 101 that disqualifies medical-process patents involving correlations between administration of a pharmaceutical and reactions in the human body – a category into which a number of such patents fall – would significantly alter the scope of § 101 in a way that is inconsistent with the legislature's own policy choices. *See Bilski*, 130 S. Ct. at 3226 (noting that "courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed'" (quoting *Diehr*, 450 U.S. at 182)). When Congress wishes to remove a particular subject matter from the broad scope of patent protection, it knows how to do so. *See* 35 U.S.C. § 287; *cf., e.g.*, Pub. L. No. 112-29 § 14(a), 125 Stat. 284, 327 (2011) (stating that "any strategy for reducing, avoiding, or deferring tax liability" is not patentable because it "shall be deemed insufficient to differentiate a claimed invention from the prior art"). Here, far from excluding medical-process patents involving methods of using pharmaceuticals, Congress has repeatedly and expressly included them.

III. Patent Protection For Medical Processes Has Spurred Innovation That Improves Patient Health

Under the regime reflected in this Court's decisions and Congress's enactments, medical innovation has thrived. The resulting inventions comprise medicines, devices, and diagnostic and therapeutic methods that have enabled physicians throughout the world to diagnose and treat many diseases. Patent protection has been – and will

continue to be – critical in spurring the progress of science in this vital area.

1. Relying on § 101, innovators have developed and patented medical processes, such as the process of using a particular drug in a particular fashion, for more than a hundred years. *See Diehr*, 450 U.S. at 183-84; *see also* Gov't Br. 15-16. Early patents for medical processes included (1) patent 4,848, issued in 1846 for surgical anesthesia with ether, (2) patent 58,034, issued in 1866 for an improved method of curing rheumatism, (3) patent 65,044, issued in 1867 for an improved method of treating "affection" of the skin, (4) patent 2,008,526, issued in 1935 for treating hepatomegaly with electrical current, and (5) patent 2,322,245, issued in 1943 for a method of transcutaneous injection.

During these early years, courts and the Board of Patent Appeals frequently upheld these types of patents. For instance, in *Dick v. Lederle Antitoxin Laboratories*, 43 F.2d 628 (S.D.N.Y. 1930), the court concluded that a method of performing operations by injecting toxin into the patient was patentable. *See id.* at 630. In *Ex parte Wappler*, 26 U.S.P.Q. (BNA) 191 (Pat. Off. Bd. App. 1935), the Board of Patent Appeals found patentable a method for shrinking living tissue. *See id.* at 192. And in *Ex parte Kettering*, 35 U.S.P.Q. (BNA) 342 (Pat. Off. Bd. App. 1936), the Board of Patent Appeals ruled that a method for producing fever in the human body was entitled to patent protection. *See id.* at 343.

In 1954, the Board of Patent Appeals expressly rejected an argument that medical processes are not

patentable subject matter. In *Ex parte Scherer*, 103 U.S.P.Q. (BNA) 107 (Pat. Off. Bd. App. 1954), the Board upheld a patent claim for a method of injecting fluid into the human body using a fluid jet rather than a hypodermic needle. The Board acknowledged that the usefulness of the claim depended on the reaction of the human body, but explained that "[t]here is nothing in the patent statute which categorically excludes such methods, nor has any general rule of exclusion been developed by decisions." *Id.* at 110. Indeed, the Board noted that in cases like *Wappler* and *Kettering* "[c]laims involving treatment of the human body have been allowed on appeal." *Id.* at 109-10.[7]

Since *Scherer*, patents for medical processes – including many patents involving the administration of a pharmaceutical or the assessment of its efficacy – have been routinely granted and upheld. *See, e.g.*, William D. Noonan, *Patenting Medical and Surgical Procedures*, 77 J. Pat. & Trademark Off. Soc'y 651, 658-60 tbl. 1 (1995) (listing representative medical-method patents); *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1225-26, 1230 (Fed. Cir. 1994) (upholding against an inventorship challenge patents for use of AZT to treat HIV). Any ruling by this Court that threatened the patentability of

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[7] *Scherer* also addressed a nineteenth-century decision that had left open "how far patents can 'invade the right of protecting health,'" Noonan, 77 J. Pat. & Trademark Off. Soc'y at 654, and – to the extent that the decision had held or implied that "medical or surgical methods are unpatentable" – expressly overruled it, *Scherer*, 103 U.S.P.Q. (BNA) at 110.

medical processes would be a radical departure from this long history of protection.

2. The availability of patents covering such medical processes has provided incentives for inventors to undertake highly expensive and risky research and development, and has therefore been critical to the advancement of medicine. At present, there are at least two areas in which medical processes involving pharmaceuticals are being used to make extraordinary advances in life-saving care-(a) processes involving new uses (also known as "indications") for existing pharmaceuticals, and (b) processes involving "personalized" medicine, in which treatment is tailored to an individual patient's physical makeup. Both of these kinds of processes are likely to involve, at some step along the way, the kind of "correlation" that Petitioners claim should not be entitled to any patent protection – for example, a correlation between the administration of an existing pharmaceutical and a reaction in the body that improves pain or cures disease, or a correlation between certain genetic or other patient characteristics and the efficacy of an existing pharmaceutical. But progress as to these kinds of processes would likely grind to a halt without stable and predictable patent protection, which offers the promise of recouping the extraordinary investments that are poured into inventing the processes and obtaining the government approval necessary to use them.

a. Today, much of the innovation in medical care comes from intensive study of possible new uses for existing medicines. Calfee, *Golden Age*, *supra*.

Where the underlying compound is already known, the compound itself is not eligible for patent protection. The "practice has therefore been to patent as a 'useful process' the use of a known drug for a recently discovered purpose." Andres Rueda, *Cataract Surgery, Male Impotence, Rubber Dentures and a Murder Case – What's so Special About Medical Process Patents?*, 9 U. Balt. Intell. Prop. L.J. 109, 146 (2001).

One example of a groundbreaking medical-process patent of this kind is the patent covering the use of AZT as a treatment for AIDS. AZT was originally developed as a cancer treatment – a role in which it "failed miserably." Philip J. Hilts, *Experimental Drug AZT Was Designed for Tumors, Skill, Luck Led to Promising Tests on AIDS*, Wash. Post, Sept. 19, 1986, at A11. It was not until two decades after AZT was first synthesized that scientists began to pursue the drug as a potential HIV treatment under patent protection for the *process* of administering the drug to HIV-positive patients. *See Burroughs*, 40 F.3d at 1225-26, 1230. This discovery was one of the first and most significant victories in the battle against AIDS.

Other examples of such innovations abound. One recent empirical study found that in some classes of medicines, 70-80% of total patient use is attributable to indications developed and approved after the drug first came to market. Ernst R. Berndt et al., *The Impact of Incremental Innovation in Biopharmaceuticals*, 24 Pharmacoeconomics (Supp. 2d) 69, 81 (2006); *see also* Said, *supra* (noting that 47% of biologics approved between 1986 and 2006

had at least one additional indication). Medical-process patents covering new uses of existing compounds include, for example, "the application of minoxidil to treat baldness, the administration of a known sugar solution (mannitol) to get drugs into the brain, and the use of a cough medicine (dextromethethorphan) to help stroke victims." *Medical Procedures Innovation and Affordability Act and Inventor Protection Act of 1995: Hearing Before the Subcomm. on Courts and Intellectual Property of the H. Comm. on the Judiciary*, 104th Cong. 67 (1995) (prepared testimony of William D. Noonan, M.D.). They also include many new indications used to treat cancer. *See* Catherine Arnst, *Same Cancer Drugs, New Applications*, Bus. Week Online, June 3, 2007, *available at* http://www.businessweek.com/technology/content/jun2007/tc20070603_510760.htm.

And further advances of this kind are on the horizon. Indeed, a "substantial amount of laboratory research conducted by pharmaceutical companies" at present involves "the expensive and painstaking evaluation of known drugs and compounds for unknown curative properties." Rueda, 9 U. Balt. Intell. Prop. L.J. at 146; *see also* Berndt et al., 24 Pharmacoeconomics at 71.

b. Personalized medicine is also an area in which extraordinary innovation is taking place. Until recently, "[d]rug selection" was "based on the average response of the patient population." Matthew Avery, *Personalized Medicine and Rescuing 'Unsafe' Drugs with Pharmacogenomics: A Regulatory Perspective*, 65 Food Drug L.J. 37, 41 (2010). Personalized medicine identifies

"biomarkers" – genetic or other biological characteristics – that permit doctors to tailor a course of treatment to a particular individual. That allows doctors to guide "medication selection and dosage regimens" to "ensure maximal drug efficiency and minimal adverse drug reaction." Teresa Kelton, *Pharmacogenomics: The Re-Discovery of the Concept of Tailored Drug Therapy and Personalized Medicine*, 19 No. 3 Health Law. 1, 1 (2007).

Correlations are the basis for this kind of personalization. People with a certain set of genetic characteristics may respond to a particular pharmaceutical when others do not; or they may require a higher dosage for the pharmaceutical to be effective, or experience a drug as toxic to their systems at lower levels than others do. Development of personalized medicine requires clinical research that identifies these correlations and permits creation of diagnostic tests to identify the relevant biomarkers. *See* Michael J. Donovon, *Legal Issues Stemming from the Advancement of Pharmacogenomics*, 14 UCLA J.L. & Tech. 1, 43-45 (2010).

Advances in personalized medicine lower costs from adverse medical events and save lives. For example, Herceptin, a long-known compound, was discovered to effectively treat an aggressive form of breast cancer – but only in the subset of breast cancer patients with an overexpression of the HER-2 protein due to a genetic anomaly. *See* Calfee, *Golden Age*, *supra*; Michael J. Shuster & Pauline Farmer-Koppenol, *Protecting Patents for Personalized Medicine*, BioPharm Int'l (Sept. 1, 2008), *available at*

http://biopharminternational.findpharma.com/biopharm/article/articleDetail.jsp?id=545358; *see also* Roche Amicus Br. 10-11. When administered to HER-2-positive breast cancer patients after surgery, Herceptin cuts the chances of a recurrence *in half*. Calfee, *Golden Age*, *supra*. By discovering the correlation and investing in the development of commercially viable diagnostic tests to identify patients with the HER-2 genes, pharmaceutical companies made it possible to personalize breast-cancer treatment so that Herceptin can be administered only to those patients likely to benefit from it. Avery, 65 Food Drug L.J. at 42; Roche Amicus Br. 10-11. An editorial in the New England Journal of Medicine called this a "revolutionary" advance that "suggests a dramatic and perhaps permanent perturbation of the natural history of the disease, maybe even a cure." Gabriel N. Hortobagyi, *Trastuzumab in the Treatment of Breast Cancer*, 353 New Engl. J. Med. 1734, 1735-36 (2005); *see also generally* Mara G. Aspinall & Richard G. Hamermesh, *Realizing the Promise of Personalized Medicine*, Harv. Bus. Rev., Oct. 2007, at 108, 111.

In light of success stories like this one, it is not surprising that pharmaceutical companies are investing significant resources in this area. A recent survey found that 12-50% of drugs in the development pipeline are personalized. Tufts Center for the Study of Drug Development, *Personalized Medicine is Playing a Growing Role in Development Pipelines*, 6 Impact Report 1, 12, Nov./Dec. 2010; *see also, e.g.*, Francis S. Collins, *Personalized Medicine: A New Approach to Staying Well*, Boston Globe, July

17, 2005, at E12 (statement by NIH director that "personalized medicine remains one of the most compelling opportunities we have to improve the odds of staying healthy").

c. Petitioners suggest that patent protection is not necessary in order for advances in medicine like these to take place – and may even prevent such advances. Pet.Br.48-58. Petitioners are wrong. Without some assurance that breakthroughs in these areas will fall within the scope of patentable subject matter, the extraordinary progress described above will likely cease, and the public will suffer.

There is no question – indeed, Petitioners concede, *see id.* at 49-50 & n.9 – that patent protection drives the development of new *compounds* used to treat human beings. Such development is highly risky, involves multiple phases of pre-clinical and clinical testing often lasting for more than a decade, and is extraordinarily costly. *See* DiMasi & Grabowski, 28 Managerial & Decision Econ. at 475-76; U.S. Dep't of Commerce, Int'l Trade Admin., *Pharmaceutical Price Controls in OECD Countries* 30-31 (Dec. 2004). Moreover, this cost must be recouped in a patent term that is often effectively much shorter than the statutory term because of the length of the regulatory review and approval process. Henry Grabowski, *Patents, Innovation and Access to New Pharmaceuticals*, 5 J. Int'l Econ. L. 849, 852 (2002). There is broad consensus that, under these expensive and difficult circumstances, innovation would not take place without the promise of patent protection – and that this is true not only with respect to start-ups, which are dependent on patents

to signal commercial viability, but also with respect to well-established companies. *See, e.g.*, *Bilski*, 130 S. Ct. at 3253 (Stevens, J., concurring) ("scholars generally agree that when innovation is expensive, risky, and easily copied, inventors are less likely to undertake the guaranteed costs of innovation"); Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 Va. L. Rev. 1575, 1615-17 (2003); Ted Sichelman & Stuart J.H. Graham, *Patenting By Entrepreneurs: An Empirical Study*, 17 Mich. Telecomm. Tech. L. Rev. 111, 157, 164 (2010).

Development of processes involving new uses for existing compounds and processes for personalized medicine involves similar challenges, and patent protection is equally necessary to ensure continued progress in these highly significant areas of innovation. Just like an initial indication, a new indication must clear regulatory hurdles, including clinical trials and approval by the FDA – and this process is costly, time consuming, and risky. Indeed, the "size and the complexity of the clinical trials for each new indication are similar to the size and the complexity of those conducted prelaunch and . . . the failure rates remain high." Said, *supra*, at 6.[8] FDA approval of a new indication for an existing pharmaceutical typically takes three to six years. *See id.* at 5. Research and development in

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[8] In some cases, the government may require additional trials or impose other costly requirements *after* it has approved a new indication. *See* FDA, *Guidance for Industry: Postmarketing Studies and Clinical Trials* (Apr. 2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf.

personalized medicine – for which a dizzying amount of data must be gathered, tested, and analyzed – is arduous in these same ways. *See* Avery, 65 Food L.J. at 43-45; Peter Huber, *Who Pays for a Cancer Drug?*, Forbes, Jan. 12, 2009, at 72; Roche Amicus Br. 10-11; *see also, e.g.*, Shuster & Farmer-Kopenel, *Protecting Patents*, *supra*.

Accordingly, medical-process patents are (like patents on the pharmaceuticals themselves) critical to spurring innovation that will save or improve countless lives. Without the promise of protection that will enable recoupment of the enormous investment that goes into development of these processes, the development will not be undertaken. *See, e.g.*, Said, *supra*, at 6 (concluding based on empirical research that patent protection drives the development of new indications); Deloitte Consulting LLP, *Avoiding No Man's Land: Potential Unintended Consequences of Follow-On Biologics* 17 (Mar. 2009) ("[i]n order for personalized medicine to become a reality, drug innovators will need a regulatory environment that allows a return on their investments"); President's Council of Advisors, *Priorities for Personalized Medicine* 21 (Sept. 2008), *available at* http://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf 21 ("The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical products, including genomics-based molecular diagnostics."); Frances Toneguzzo, *Impact of Gene*

Patents on the Development of Molecular Diagnostics, 5 Expert Op. Med. Diag. 273, 275 (2011) ("[f]or validation of molecular diagnostics, patents are critical to incentivize the significant investment required"); *see also* Grabowski, 5 J. Int'l Econ. L. at 850-53; Rueda, 9 U. Balt. Intell. Prop. L.J. at 132 ("Without intellectual property protection, companies and individuals who otherwise may have poured time and resources towards medical process research may not do so."). In an area so fraught with uncertainty, the stability and certainty of patent protection is absolutely critical.

Of course, a company that owns the patent on a pharmaceutical compound already has some incentive to research additional indications – but that incentive is unlikely to be sufficient. The approval process for a second indication frequently takes long enough that the patent period for the original compound has run or nearly run, leaving no possibility of obtaining a meaningful return on investment. *See* Said, *supra*, at 3-4; Martin, 82 J. Pat. & Trademark Off. Soc'y at 396. Moreover, innovations related to new uses for existing drugs frequently happen at the hands of companies that did not discover the compound in the first place. *See, e.g.*, *Burroughs*, 40 F.3d at 1225. Such companies can protect their investment in innovation only by patenting the *process*.

Petitioners try to counter these weighty concerns by contending that academic research is inhibited by patent protection for medical processes. Pet.Br.52-56. Academic research does not generally put life-saving tests and treatments in the hands of patients;

the tremendous investments described above are necessary to do that. *See, e.g.*, *Burroughs*, 40 F.3d at 1225-26 (explaining that while AZT's effects on HIV were first demonstrated in NIH research, the investment of a biotechnology firm turned the drug into a useful treatment for the disease). In any event, however, Petitioners' suggestion is without any basis – and, indeed, empirical research suggests that patent protection is no bar to academic advances. According to one study, only 1% of academic respondents reported a project delay of more than a month due to patents on inputs necessary for their research; none reported abandoning a research project due to the existence of patents. John P. Walsh et al., *Final Report to the National Academy of Sciences' Committee Intellectual Property Rights in Genomic and Protein-Related Inventions: Patents, Material Transfers and Access to Research Inputs in Biomedical Research* (Sept. 20, 2005), *available at* http://www2.druid.dk/conferences/viewpaper.php?id+776&cf=8; *see also, e.g.*, Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 Hous. L. Rev. 1059, 1061 (2008) (collecting empirical research), *cited in* Pet.Br.55; Richard Epstein, *Heller's Gridlock Economy in Perspective: Why There Is Too Little, Not Too Much Private Property*, 63 Ariz. L. Rev. 51, 77-78 (2011); Roche Amicus Br. 21-27.[9]

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[9] In addition, the mere fact that a medical process falls within the scope of patentable subject matter does not mean that a

In fact, just the opposite is true. Patent disclosures educate the research community on important advances and spark additional progress. Patents make the exchange or acquisition of knowledge more efficient and less costly, allowing the scientific community to learn from the successes and failures of others. *See Scott Paper Co. v. Marcalus Mfg. Co.*, 326 U.S. 249, 255 (1945); Epstein, 63 Ariz. L. Rev. at 80; *see generally* Letter from Sir Isaac Newton to Robert Hooke (Feb. 5, 1675), *reprinted in* Robert K. Merton, *On The Shoulders of Giants: A Shandean Postscript*, at ii (1965) ("[i]f I have seen further [than you and Descartes] it is by standing on ye sho[u]lders of Giants"). And many advances take place when researchers try to "invent around" an existing patent, finding new (and perhaps better and cheaper) ways to achieve results. *See, e.g., State Indus., Inc. v. A.O. Smith Corp.*, 751 F.2d 1226, 1235-36 (Fed. Cir. 1985) (explaining that the "'negative incentive' to 'design around' a competitor's products" brings "a steady flow of innovations to the marketplace").

Accordingly, it is clear that disrupting expectations of patent protection in medical processes will severely restrict important medical gains. As one author succinctly explains, "[t]he surest way to hobble medical technology" – particularly with respect to new areas where great advances in medicine are currently being made – "is to damage intellectual property (IP) protections, mainly patents." Calfee, *Golden Age*, *supra*.

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patent will issue, or survive a challenge; the patent statute sets up a number of other hurdles. *See infra* pp. 28-30.

IV. Petitioners' Approach Destabilizes This Regime And Undercuts Incentives For Innovation

While purporting to rest on this Court's existing precedents, Petitioners call into question the long-established regime that has given rise to these important medical advances. While Petitioners do not clearly state any one test for determining whether something is patentable subject matter, their approach departs from precedent in at least three important respects: (1) it imports into the § 101 analysis an inquiry into the novelty of the invention that is mandated by different provisions in the statute and that should be carried out only after the "coarse filter" of § 101 is applied; (2) it breaks apart a process claim into its individual steps, and examines each step separately to assess whether a natural law is at play; and (3) in the guise of an inquiry about the scope of "preemption," it gives primacy to policy considerations that are properly within the province of the legislature.[10] Were this Court to adopt any of these three aspects of Petitioners' approach, the resulting changes to an area in which "it is especially important that the law remain stable and clear," *Bilski*, 130 S. Ct. at 3231 (Stevens, J., concurring), would disrupt the "settled expectations of the inventing community," and therefore severely undercut the incentives for

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[10] In addition, as discussed above, Petitioners err in assuming that the metabolite correlations at issue in this case, which result from a man-made pharmaceutical, are a natural phenomenon. *See supra* p. 7.

medical innovation, *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 739 (2002).

1. This Court should reject Petitioners' attempt to import into § 101 the separate limits set forth in 35 U.S.C. §§ 102 and 103. Section 102 embodies the "anticipation" doctrine, barring a patent on an invention that was already known, used, described, or patented. 35 U.S.C. § 102. Section 103 bars a patent that is different from the prior art "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill." *Id.* § 103.

Petitioners repeatedly argue that Prometheus's patent does not satisfy the requirements of § 101 because the bulk of the claims at issue are insufficiently innovative. Petitioners assert, for example, that doctors "considered metabolite levels on their own years before these patent claims were filed," Pet.Br.25; that the "administration and testing steps are 'well known' and 'long prevalent' in medical practice," *id.* at 35; that respondents "did not invent the drug," *id.* at 37 n.7; and that the patent makes only a "minimal contribution to medicine," *id.* at 40.

These attacks on Prometheus's patent are not in any way addressed to separating invention from nature, as § 101 requires. *Chakrabarty*, 447 U.S. at 313. But Petitioners insist that because "Section 101 on its face limits patentable subject matter to a 'new

and useful process,'" this reasoning is consistent with the statute. Pet.Br.36.

This Court has already squarely rejected that argument. As the Court explained in *Diamond v. Diehr*, 450 U.S. 175 (1981), the question "of whether a particular invention is novel is *wholly apart from whether the invention falls into a category of statutory subject matter*." *Id.* at 190 (emphasis added) (internal quotation marks omitted). That is because the "new and useful" language in § 101 is by its own terms only "a general statement of the type of subject matter that is eligible for patent protection 'subject to the conditions and requirements of this title.'" *Diehr*, 450 U.S. at 189 (quoting § 101). Highly "[s]pecific conditions for patentability follow" in the subsequent provisions, and Congress plainly intended those to control any determination of whether the invention is new or useful. *Id.*; *see also id.* at 191, 193 n.15.

These separate conditions are stringent, and the obviousness doctrine in particular is a substantial hurdle that not all would-be inventors will overcome. That is especially true with respect to patents in the biological arena, since "the requirement that an invention must be a 'nonobvious' advance to be patentable is particularly strictly applied in all the biological examining groups" at the Patent Office. Noonan, 77 J. Pat. & Trademark Off. Soc'y at 661. Indeed, "[t]he likelihood that a biological patent application will successfully issue as a patent is about one-half of the likelihood of success in conventional mechanical and electrical cases," and the patents that do emerge from "this rigorous

patenting process" are generally "narrow in scope." *Id.* Courts also often invalidate patents for obviousness when they are challenged in litigation. *See* Jennifer Nock & Sreekar Gadde, *Raising the Bar for Nonobviousness: An Empirical Study of Federal Circuit Case Law Following* KSR, 20 Fed. Cir. B.J. 369, 392 (2010). Accordingly, process patents that do no more than recite traditional medical tests or treatment courses will not survive obviousness review.

This analysis should be carried out under the specific requirements of the relevant statutory provision, however, and not transformed into some sort of free-floating assessment that is liable to depart from the rules that Congress has laid down in §§ 102 and 103. Lest the inquiry come unmoored from the "conditions and requirements" of the statute, 35 U.S.C. § 101, the patent eligibility analysis is – and should remain – "only a threshold test," *Bilski*, 130 S. Ct. at 3225; *see also Flook*, 437 U.S. at 588 (explaining that the patent-eligibility inquiry "does not involve the familiar issues of novelty and obviousness that routinely arise under §§ 102 and 103 when the validity of a patent is challenged"); Gov't Br. 16-17.

2. Together with their efforts to use the term "new" in § 101 to import an obviousness inquiry, Petitioners also seek to change the law in another way: by breaking apart a patent claim into small parts and then testing each part separately against § 101. Thus, Petitioners characterize most of the claim steps at issue here as obvious and the remaining step as embodying a natural law – and

insist that the entire claim should therefore be barred under § 101. Pet.Br.33-35 (characterizing part of the claim as a correlation that counts as a "natural phenomenon" and claiming that the "determining" and "administering" steps are invalid for "independent reasons").

Certain *amici* also suggest that a patent claim need not be read as a whole for purposes of the § 101 inquiry. For instance, the ACLU argues that only a portion of a claim – whatever a court determines after the fact to be its "essence" – should be determinative of patentability under § 101, with the other portions "stripped away." ACLU Br. 11. Although this argument is stated differently than Petitioners', it amounts to the same thing: a request that this Court endorse a new and piecemeal approach to assessing a patent claim under § 101.

That approach is deeply flawed. As this Court has explained, there is a law of nature at work somewhere in every patent – perhaps most noticeably in ones that are permissible *applications* of such a law. *See, e.g.*, *Funk Bros.*, 333 U.S. at 135 (Frankfurter, J., concurring) ("Everything that happens may be deemed 'the work of nature,' and any patentable composite exemplifies in its properties 'the laws of nature.'"); *see also Diehr*, 450 U.S. at 189 n.12 ("all inventions can be reduced to underlying principles of nature"); Pet.App.17a ("quite literally every transformation of physical matter can be described as occurring according to natural processes and natural law"). For instance, the kinds of medical-process patents described above regarding new indications and personalized medicine, which

are adding immeasurably to the quality of patient care, involve such laws to the extent that they depend on chemical reactions and other basic scientific principles. Were it permissible to search for the law of nature hidden somewhere within a patent claim, then virtually every patent could conceivably be drawn into question under § 101.

For that reason, this Court has definitively stated that it is "inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 188); *see also id.* (emphasizing "need to consider the invention as a whole" in carrying out the § 101 inquiry). Indeed, analyzing a claim's elements together is "particularly" important "in a process claim because a new combination of steps in a process may be patentable even though all the constituents of the combination were well known and in common use before the combination was made." *Diehr*, 450 U.S. at 188.

That rule is consistent with blackletter principles of patent law that are deeply embedded in the way that drafters and interpreters of patent claims approach their tasks. It is axiomatic that in interpreting a patent claim all of its elements must be considered, and none can be viewed in isolation. It is likewise axiomatic that an accused product or method does not infringe unless it satisfies each and every element of a claim. *See, e.g.*, 5A *Chisum on Patents* § 18.03(4)(a) (2007). Petitioners' approach of breaking a claim into its building blocks, and then insisting that the claim is invalid if any one of those

blocks can be characterized as a law of nature (or as falling within one of the other exceptions associated with § 101), is irreconcilable with these well-established doctrines.

Petitioners try to fall back on statements in the caselaw that the § 101 exceptions "'cannot be circumvented by . . . adding 'insignificant postsolution activity,'" *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 191-92), or mere "data gathering" steps, *In re Meyer*, 688 F.2d 789, 794 (C.C.P.A. 1982); *see, e.g.*, Pet.Br.35. But those admonitions cannot justify any effort to carve up a claim in which the various steps are so bound up with each other. In Prometheus's patent, it is the administration of the pharmaceutical that *creates* the metabolites in the first place, and the determining step that allows those new metabolites to be quantified – and both of these are necessary in order for a physician to be advised that metabolite levels are too low or too high to treat the family of diseases at which the patented method is directed.

The Federal Circuit's opinion appropriately emphasized this connection between the different steps of the claim. The court of appeals explained that "transformation is central to the purpose of the claims" since "[m]easuring the levels of [the metabolites] is what *enables* possible adjustments to thiopurine drug dosage to be detected for optimizing efficacy or reducing toxicity during a course of treatment." Pet.App.19a (emphasis added). The court correctly concluded that due to "the integral involvement of the administering and determining steps in Prometheus's therapeutic methods, this case

is easily distinguishable from prior cases that found asserted method claims to be unpatentable for claiming data-gathering steps and a fundamental principle." *Id.* at 20a; *see also* Gov't Br. 15 (explaining that final portions of the claim at issue "are premised upon[] the transformation of the patient's body chemistry that the administering step entails").

Accordingly, this Court should rebuff Petitioners' effort to change the law requiring unitary treatment of a claim. That change would create tremendous uncertainty about whether medical-process claims – and many other types of claims – are subject to protection under § 101, and thereby deprive the patent regime of the stability and flexibility necessary to promote innovation. *See Chakrabarty*, 447 U.S. at 316.

3. Finally, Petitioners assert that the patent eligibility of a process involving a natural phenomenon turns on whether the claim "confine[s]" its "field of preemption." Pet.Br.34, 35, 38-39; *see also id.* at 48 (asserting that "the likely effect of a [particular] patent on innovation and competition has an important bearing on the patent's validity"). Again, this approach would represent a significant and deleterious change in the law and introduce considerable uncertainty. "Preemption" is a concern that animates the application of the traditional test distinguishing between human ingenuity and the products of nature. But it is not an appropriate test in and of itself – because it is impossible to judge whether the scope of preemption associated with a particular claim is too broad without engaging in

unconstrained policy judgments of the kind that are best left to Congress.

As an initial matter, it is important to note that Petitioners' premise here is wrong: the Prometheus patent, like other processes involving pharmaceuticals, does not have an unlimited preemptive effect. Patents relating to *particular* pharmaceuticals – and the non-natural products that they create in the human body – are inherently limited in scope. *Compare Lab. Corp. of Am. v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006) (Breyer, J., dissenting) (discussing naturally occurring metabolites). And the complexity of biological systems means there are generally multiple pathways for understanding and treating diseases.[11]

In any event, however, it is clear that an invention is not ineligible for patent protection just because it has sweeping implications. To the contrary, highly valuable inventions historically have been granted patent protection, even if – for a limited time – they dominate a field of endeavor. *See, e.g.*, U.S. Patent No. 214,636 (Thomas Edison's light bulb); U.S. Patent No. 821,393 (Wright Brothers' flying machine).

The patent system provides the stimulus for such human ingenuity and recognizes its long-term benefit to society. Indeed, to the extent that broad

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[11] *See, e.g.*, David E. Adelman, *A Fallacy of the Commons in Biotech Patent Policy*, 20 Berkeley Tech. L.J. 985, 1010-17 (2005). Indeed, many recent drugs with multiple new uses have quickly spawned competitor drugs with similar characteristics. Calfee, *Golden Age*, *supra*.

medicine-related patents issue (despite the strictures of patent examining in this area, *see supra* pp. 29-30) and are not licensed, there is a substantial economic literature suggesting that society still benefits because "innovation would drop substantially in the pharmaceutical industry in the absence of effective patent protection." Burk & Lemley, 89 Va. L. Rev. at 1617; *see also* James W. Hughes et al., "Napsterizing" Pharmaceuticals: Access, Innovation, and Consumer Welfare (Nat'l Bureau of Econ. Res., Working Paper No. 9229, 2002) (finding that eliminating patent protection on pharmaceuticals would cost future consumers three dollars in lost benefits for every dollar saved in reduced drug prices); *supra* pp. 21-23. Accordingly, patentability for a valuable biotechnology invention should not be vitiated because of its perceived "expense" during the short period of patent exclusivity.

Were this Court to adopt the approach that Petitioners urge, lower courts would be forced to engage in what is essentially a policy-based analysis in order to decide questions of patentability under § 101, asking in the most general terms whether the patent at hand sweeps too broadly and covers things that society would prefer to remain unencumbered. It is hard to imagine anything more likely to engender uncertainty and confusion among would-be inventors, and thus to discourage inventions that require significant up-front risk and investment of time and money – as do societally beneficial medical-process inventions.

In addition, beyond the basic inquiry about whether a patent claim (read as a whole) falls into

one of the three § 101 exceptions, making judgments about patent-eligible subject matter is a task that falls within Congress's area of expertise. As discussed above, Congress knows how to remove certain subject matter from the scope of patent protection, and has already addressed the policy considerations surrounding pharmaceutical-related medical-process patents. *See supra* pp. 12-13. Any further restrictions should be debated by the legislature, not imposed by courts making *ad hoc* judgments on a patent-by-patent basis about the costs and burdens of exclusivity. *See Chakrabarty*, 447 U.S. at 317 ("Whatever their validity, the contentions . . . pressed . . . should be addressed to the political branches of the Government, the Congress and the Executive, and not to the courts.").

CONCLUSION

For the foregoing reasons, *amicus* respectfully submits that the judgment of the Federal Circuit should be affirmed.

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AMICUS CURIAE BRIEF

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES)
AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

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Respondent.

ON WRIT OF CERTIORARI TO THE
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BRIEF FOR AMICI CURIAE ROCHE MOLECULAR SYSTEMS, INC., VENTANA MEDICAL SYSTEMS, INC., HOFFMANN-LA ROCHE INC., AND ABBOTT LABORATORIES, INC. IN SUPPORT OF NEITHER PARTY

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INTEREST OF AMICI CURIAE[1]

Amici curiae are leading biopharmaceutical companies and pioneers in the new clinical frontiers of molecular diagnostics and personalized medicine. As both

[1] No counsel for a party authored this brief in whole or in part, and no persons or entities, other than amici or their counsel, made a monetary contribution to the preparation or submission of this brief. Letters from the parties consenting to the filing of this brief are on file with the Clerk.

purchasers and sellers of patented diagnostic technologies, *amici* have a uniquely balanced perspective on the issues of public policy raised in this case.

Roche Molecular Systems, Inc., Ventana Medical Systems, Inc., and Hoffmann-La Roche Inc. are affiliates of F. Hoffmann-La Roche Ltd (collectively "Roche"), the world's largest biopharmaceutical company. Close cooperation within Roche's pharmaceutical and diagnostic divisions enable it to tailor treatments to specific patient subpopulations based on the latest scientific understanding of biology and disease at the molecular level. Roche develops and manufactures a wide array of innovative diagnostic products used in the diagnosis, prognosis, and treatment of cancer and infectious diseases. Some of Roche's diagnostic tests utilize the company's Nobel Prize-winning polymerase chain reaction ("PCR") technology to detect the genetic material (DNA or RNA) in cancerous cells and infecting pathogens, such as HIV or hepatitis. Because the tests are capable of identifying and characterizing disease earlier and more specifically than tests based on the body's immune response, patients can be treated and monitored with great precision. Roche's tissue-based diagnostic tests enable the detection of genetic biomarkers that facilitate the ability of health care providers to prognose or even predict patient outcomes for various cancer therapeutic regimens. Roche has a broad line of oncology, virology, microbiology and blood screening tests, which are used by researchers, physicians, patients, hospitals, laboratories and blood banks around the world.

Abbott Laboratories, Inc. ("Abbott") is a diverse, global health care company with scientific expertise and products that address the full range of health care needs—from disease prevention and diagnosis to treatment and cure. For more than 120 years, Abbott has

been a pioneer in developing innovative solutions that improve health and the practice of health care. Among other things, Abbott develops and markets tests that can detect subtle but key changes in patients' genes and chromosomes. These award-winning technologies permit earlier detection and diagnosis of diseases; assist in the selection of therapies that are more likely to prove effective; and improve the monitoring of disease progression. Abbott offers more than 350 products related to molecular diagnostics for infectious disease, oncology, genetics and automation, including breakthrough DNA probe technologies critical to the diagnosis and treatment of lung, breast, and bladder cancer.

Roche and Abbott invest billions of dollars annually in the research and development of diagnostic products and technologies. Patent protection is not merely critical to prevent free-riding on their substantial investments. It is necessary to provide appropriate incentives to invest in research, development, and innovation in areas like personalized medicine that hold the greatest promise for improving treatment and decreasing the costs of therapy for those suffering from often fatal diseases. The question presented in this case is therefore of great significance to both Roche and Abbott.

SUMMARY OF ARGUMENT

Patent protection is critical to the development of personalized medicine, which promises not only to improve patient health dramatically but also to curb the costs of providing safe and effective treatments. Denying patents for novel and nonobvious diagnostic tests ill-serves the Patent Act's purposes and Congress's goals in establishing the limits of patent eligibility under 35 U.S.C. § 101.

I. Personalized medicine is a new and revolutionary field that promises dramatic improvements in how we diagnose and treat disease. Rather than treat all cases of a particular disease identically, personalized medicine seeks to tailor diagnosis and treatment to each patient's unique genomic or molecular profile. The essence of personalized medicine is the use of diagnostic tests to identify certain biological traits or "biomarkers" that are associated with particular disease characteristics. For example, patients with a particular "biomarker" may respond to a specific treatment, whereas those lacking that marker will not. Identification of those biomarkers thus can form the basis for diagnostic or therapeutic decision-making. Government regulators, academics, and industry stakeholders have all recognized that the widespread adoption of personalized medicine promises to transform health care by improving patient care and reducing the costs associated with unnecessary or ineffective treatment.

II. Patent protection is essential to realizing the promise of personalized medicine. The discovery and validation of clinically useful biomarkers requires expensive and risky clinical trials, much like those in the biotechnology and pharmaceutical industries. Translating those discoveries into commercially viable diagnostic tests further requires demonstrating to regulators and insurers the clinical utility and cost-effectiveness of those tests. Given the significant investment and substantial risk entailed in the discovery, development, implementation, and regulatory approval of diagnostic tests, the incentives afforded by the patent system are critical to ensuring the growth of the personalized medicine industry in the United States.

III. The criticisms of patents for diagnostic tests are theoretical and unsupported by empirical evidence.

Patents in this field do not stifle innovation or frustrate the practice of medicine. The limited period of exclusivity afforded by patents provides the necessary incentives for prospective research, development, and commercialization of diagnostic tests, which greatly serve the long-term public interest. In the personalized medicine industry, as in the biopharmaceutical industry generally, market-driven business practices and self-enforcing market norms correct for any perceived limitations on the accessibility of patented diagnostic technologies. In any event, Congress has already spoken on the issue by exempting certain researchers and medical practitioners from liability for patent infringement. To the extent additional protections prove desirable, Congress retains the ability to refine the existing exemptions based on sound evidence and with due regard to the reliance interest of existing patent holders.

ARGUMENT

I. PERSONALIZED MEDICINE IS A NASCENT FIELD THAT PROMISES TO REVOLUTIONIZE THE HEALTH CARE INDUSTRY

A. Testing And Analysis Of Molecular Biomarkers Allows Doctors To Customize Disease Prevention, Diagnosis, And Treatment

Physicians, clinicians, and researchers have long recognized that people with the same disease often respond very differently to the same treatment. Traditional medicine relies on a trial-and-error approach to that problem. On average, less than half of patients respond positively to prescription medications; for the remainder, the drug is either ineffective or toxic. Spear et al., *Clinical Application of Pharmacogenetics*, 7 Trends Molecular Med. 201, 201-202 (2001); *see also* Phillips et al., *Potential Role of Pharmacogenomics in*

Reducing Adverse Drug Reactions: A Systematic Review, 286 J. Am. Med. Ass'n 2270, 2270 (2001) (adverse drug reactions are among the leading causes of death in the United States). As a result, scarce resources are wasted on the purchase of medicines that either do no good or actually harm the patient. Worse still, effective treatments are not implemented unless and until they are identified through a wasteful and potentially painful trial-and-error process.

Personalized medicine provides substantial progress in this regard by identifying, in advance, the treatments that will and will not likely work. Defined as the science and practice of customizing the prevention, diagnosis and treatment of disease based on molecular "biomarkers," such as gene sequence variations, gene or protein expression levels, or metabolites, personalized medicine represents one of the most promising new clinical frontiers. *See* Personalized Medicine Coalition, *The Case for Personalized Medicine* 2-4 (2009), *available at* http://www.personalizedmedicinecoalition.org/sites/default/files/TheCaseforPersonalizedMedicine_5_5_09.pdf ("*The Case for Personalized Medicine*").[2]

At its core, personalized medicine involves the use of diagnostic tests to obtain information about molecular biomarkers that are correlated with particular disease characteristics. *The Case for Personalized Medicine* 4. If the test results show that a patient possesses particular biomarkers, that information can be used for

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[2] Others define "personalized health care" and "personalized medicine" in different, often broader terms. *See, e.g.*, PricewaterhouseCoopers LLP, *The New Science of Personalized Medicine: Translating the Promise into Practice* 3, 8 (Oct. 2009).

purposes of diagnosis, prognosis, predicting the future risk of disease, or selecting treatment regimens that are particularly suited to that patient. *Id.* at 4-7. For example, a particular biomarker may indicate the early presence of a particular disease, permitting effective treatment before symptoms even appear. Another may indicate that certain treatments will work most effectively, signaling that others can be safely disregarded as ineffectual or potentially harmful. *See infra* Section I.B. (providing specific examples).

Personalized medicine thus has the potential to decrease the incidence of adverse drug reactions dramatically. Physicians and clinicians are guided by custom-designed genetic or molecular tests that permit superior diagnostic and therapeutic decision-making. *The Case for Personalized Medicine* 4-5. Health care costs decline as well. Insurers are not saddled with the costs of needless tests and/or treatment regimens that later prove to be unnecessary at best. *Id.* at 6-7. Most importantly, patients receive an early diagnosis, followed by highly individualized treatment that maximizes efficacy while minimizing the potential for side effects and adverse reactions. *Id.* at 4-6.

B. Personalized Medicine Is A Rapidly Developing Field In Which Industry Participation And Collaboration Is On The Rise

As leaders in this field, *amici* have developed diagnostic tests and associated treatments that promise to save lives, prevent needless suffering, and save billions of health care dollars. Roche, for example, has designed a microarray device called the Amplichip® CYP450, which provides comprehensive detection of gene variations—including deletions and duplications—for the CYP2D6 and CYP2C19 genes. The Am-

pliChip® test assists physicians in determining the best therapeutic strategy and treatment dose for an estimated 25% of all prescription drugs, including many common psychiatric drugs (antipsychotics and antidepressants). Abbott's Urovysion Bladder Cancer test identifies genetic aberrations in urine specimens from persons with hematuria (blood in urine), allowing the early detection of bladder cancer before any morphological changes manifest, which can dramatically increase survival rates. Other biopharmaceutical companies have developed diagnostic tests that permit more accurate prognoses. Genomic Health, Inc., for example, markets the OncoType DX®, which predicts the likelihood of breast cancer recurrence and patient survival within 10 years of diagnosis. *See, e.g.*, Hornberger et al., *Economic Analysis of Targeting Chemotherapy Using a 21-Gene RT-PCR Assay in Lymph-Node-Negative, Estrogen-Receptor-Positive, Early-Stage Breast Cancer*, 11 Am. J. Managed Care 313 (2005).

The promise of innovations in this area is also reflected in new AIDS detection techniques. For example, the new fourth-generation Architect® HIV Ag/Ab Combo detects infections 7 to 20 days earlier than prior HIV antibody tests. It was the first FDA-approved test for the diagnosis of HIV-1 and -2 infections in pregnant women and children under two. Early detection of AIDS is obviously critical not merely to its treatment, but also to preventing its spread.

One area of personalized medicine that has garnered significant interest in recent years is "companion diagnostics," which are a special class of diagnostic tests used to identify the patients most likely to benefit from a particular drug. *See* Food and Drug Administration ("FDA"), *Draft Guidance for Industry and Food and Drug Administration Staff—In Vitro Com-*

panion Diagnostic Devices 6-7 (July 14, 2011) ("FDA, *Draft Guidance*") (defining companion diagnostic as a "diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product.").

Roche recently received FDA approval to commercialize its cobas® 4800 BRAF V600 Mutation Test, a diagnostic test that identifies patients who would benefit from the Roche drug Zelboraf®, which is indicated for the treatment of certain types of inoperable or metastatic melanoma.[3] The FDA has also recently approved a new molecular diagnostic test—Abbott's Vysis ALK Break Apart FISH Probe—for detecting rearrangements of the anaplastic lymphoma kinase (ALK) gene in non-small-cell lung cancer (NSCLC). That test identifies a genetic variation (the ALK fusion gene) that indicates a high likelihood that a patient will respond positively to Pfizer's XALKORI® (crizotinib) therapy. These breakthroughs in the advancement of personalized medicine—and companion diagnostics specifically—permit cancer treatments that are custom-tailored to patients' unique genetic profiles. By excluding patients who would not benefit from particular treatment, the companion diagnostics developed by

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[3] Zelboraf® and its companion diagnostic were cited by the FDA as a "great example of how companion diagnostics can be developed and used to ensure patients are exposed to highly effective, more personalized therapies in a safe manner." Press Release, FDA, *FDA Approves Zelboraf and Companion Diagnostic Test for Late-Stage Skin Cancer* (Aug. 17, 2011), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm268241.htm.

Roche, Abbott, and others in the industry also save health care dollars and prevent needless suffering.[4]

The development and commercialization of these diagnostic tests, and companion diagnostics in particular, is often a collaborative process that entails sharing of clinical samples, data, and other information among various industry participants. For example, Roche and Abbott together made one of the first significant advances in this area, leveraging the power of a companion diagnostic in connection with Herceptin® (trastuzumab). *See* PricewaterhouseCoopers LLP, *The New Science of Personalized Medicine: Translating the Promise into Practice* 7 (Oct. 2009). Herceptin® is a drug developed by Roche's affiliate Genentech, Inc., to treat a particularly aggressive form of breast cancer. Although only a small portion of those suffering from breast cancer will benefit from Herceptin®, for that subpopulation the drug is extraordinarily effective, increasing survival periods by an average of 25%. It is also highly effective in lowering the risk that early-stage breast cancer will return. *Id.*

Because of personalized medicine, Herceptin® treatment can now be targeted to the subset of the population for whom it has that life-saving and life-extending potential. Abbott developed and commercialized the first diagnostic test to identify those patients who exhibit over-expression of a protein known as human epidermal growth factor receptor type 2 ("HER-2") due to a genetic anomaly. That overexpression of the HER-2 protein is associated with certain particularly aggressive cancers.

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[4] Other examples of life-saving companion and molecular diagnostics abound. A more comprehensive list may be found in *The Case for Personalized Medicine* at 18.

Most importantly, it also predicts whether the patient will have a dramatic response to treatment with Herceptin®. Thus, HER-2 companion diagnostics not only identify patients who will respond to Herceptin®, it also helps identify patients who will not, avoiding the costs and life-threatening delays associated with unnecessary Herceptin® treatment. *See* Hillner & Smith, *Do the Large Benefits Justify the Large Costs of Adjuvant Breast Cancer Trastuzumab?*, 25 J. Clinical Oncology 611, 612 (2007); *see generally* Dendukuri et al., *Testing for HER2-positive Breast Cancer: A Systematic Review and Cost-Effectiveness Analysis*, 176 Can. Med. Ass'n J. 1429 (2007). More recently, the FDA approved Roche's new tissue-based genetic test for the measurement of HER-2 in breast tumor tissue, which uses standard light microscopy. Unlike prior fluorescence diagnostics, Roche's new light microscopy-based HER-2 test can be performed in a standard laboratory, improving the accessibility of HER-2 testing for patients worldwide.

The development of companion diagnostics for Herceptin® illustrates the success of personalized medicine and the promise it holds for the future of the health care industry. Herceptin® and its companion diagnostic tests for HER-2 have had a major impact in the treatment of cancer, including metastatic breast cancer. *See* Tan & Swain, *Ongoing Adjuvant Trials with Trastuzumab in Breast Cancer*, 30 Seminars in Oncology 54, 54 (2002). Absent the promise of patent protection, there would be little incentive for biopharmaceutical companies to develop and market either an initial diagnostic test or improved, next-generation methods of detecting such potentially fatal diseases.

C. Personalized Medicine Is Expected To Have A Significant Impact On The Future Of Health Care In The United States

Personalized medicine has become a priority health care issue at the highest levels of government. Following a wide-ranging review of the field, the President's Council of Advisors on Science and Technology concluded that "personalized medicine warrants significant public and private sector action to realize the development and introduction into clinical practice of this promising class of new medical products." President's Council of Advisors on Science and Technology, *Priorities for Personalized Medicine* 1 (Sept. 2008) ("*Priorities for Personalized Medicine*"). The current Director of the National Institutes of Health ("NIH") has observed that "personalized medicine remains one of the most compelling opportunities we have to improve the odds of staying healthy." Collins, *Personalized Medicine: A New Approach to Staying Well*, Boston Globe, July 17, 2005, at E12.

Congress and the Executive Branch have begun laying the foundation for investment in research and infrastructure necessary to support a rapid expansion in personalized medicine over the coming decades. In 2006, the Department of Health & Human Services ("HHS") launched the "Personalized Health Care Initiative" for the purpose of coordinating "activities in HHS agencies that could help accelerate a personalized health care future." HHS, *Personalized Health Care: Pioneers, Partnerships, Progress* 13 (2008) ("HHS, *Personalized Health Care*"). One of the key priorities of the FDA is to "stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes." FDA, *Advancing Regulatory Science at FDA: A Strategic Plan* 10-13 (Aug. 2011). This past

year, NIH and FDA announced "a new collaboration on regulatory and translational science to accelerate the translation of research into medical products and therapies ... to help make personalized medicine a reality." Hamburg & Collins, *The Path to Personalized Medicine*, 363 New Eng. J. Med. 301, 304 (2010).

Congress recently enacted legislation that calls for improvements in health care services through comparisons of the effectiveness of various treatments in patient subpopulations. *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 3011, 3013, 3113, 6301, 124 Stat. 119, 378-79, 381-82, 422, 727-28 (2010).[5] Such initiatives are intended to set the stage for further research and development activities that will increase the number of diseases and treatments for which commercial diagnostic tests are available. Garber & Tunis, *Does Comparative-Effectiveness Research Threaten Personalized Medicine?* 360 New Eng. J. Med. 1925, 1925 (2009).

II. PATENTS ARE CRUCIAL TO PROVIDING PROPER INCENTIVES TO INVEST IN PERSONALIZED MEDICINE AND RELATED ADVANCES

A. Commercialization Of A Diagnostic Test Requires Substantial Investment In Research And Development

The biotechnology industry relies heavily on patent protection to encourage the investments necessary to convert inventions that might otherwise exist only on

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[5] Personalized medicine was also the subject of earlier congressional efforts at health care reform. *See, e.g.*, Genomics and Personalized Medicine Act of 2007, S. 976, 110th Cong. (2007); Genomics and Personalized Medicine Act of 2008, H.R. 6498, 110th Cong. (2008).

paper into commercially viable products that improve the health and quality of life of the public. Many of these inventions are based on clinical data that lead to the correlation of one or more biomarkers with disease prognosis or predictive response to a therapeutic—the heart of personalized medicine.

In 2011, publicly-traded companies in the United States alone invested more than $22 billion in biotechnology-related research and development. Ernst & Young, *Beyond Borders: Global Biotechnology Report* 37-39 (2011). The average cost of bringing a single biotechnology-related therapeutic to market, including basic research, clinical trials, and post-approval testing, exceeds $1.2 billion. Grabowski, *Follow-On Biologics*, 7 Nature Reviews Drug Discovery 479, 482 (2008). For every successful product, many more are abandoned, often only after substantial investments that cannot be recouped. *Id.* at 481 (only 30% of biological therapeutics that make it as far as human trials succeed); *see generally* Graham et al., *High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey*, 24 Berkeley Tech. L.J. 1258, 1277, 1288, 1290 (2009) (finding that patents are considered important to innovation in the biotechnology and medical device sectors). Investments in this area can be justified only if the returns on successful products are sufficient to cover the costs of developing not merely those products but also the many more that end in failure.

Much like in the biotechnology industry generally, the research and development activities needed to make advances in personalized medicine are extremely costly. To make a molecular biomarker such as a genetic sequence clinically useful, the first task is to find associations between the biomarker and a disease or

drug response. "Such studies usually require thousands of participants and the collection and preservation of a large number of biological specimens and genetic material, and as such can go well beyond the resources of a single company or laboratory." *The Case for Personalized Medicine* 9. Once the association has been discovered, clinical trials are required to demonstrate and validate the clinical utility of the association. Many such trials are equivalent to pharmaceutical trials in both design and scope, sometimes involving following patients for years to determine long-term safety and efficacy. *See generally* HHS, *Personalized Health Care* 83. Bringing a single diagnostic product to market typically requires tens of millions of dollars and can cost well over $100 million under certain circumstances, an investment coupled with several years of research and clinical studies involving hundreds of patients. *See, e.g., id.* at 84-85.[6]

Finding the private capital needed to fund the clinical research required to discover and validate a broader array of biomarkers is one of the greatest challenges facing the personalized medicine industry. *See* HHS, *Personalized Health Care* 83. Diagnostic products generally offer a very low rate of return on investment, particularly in light of the staggering amounts required for their development. *Id.* at 83-85; *see generally* Kling, *Diagnosis or Drug? Will Pharmaceutical Companies or Diagnostics Manufacturers Earn More from Personalized Medicine?*, 8 EMBO Rep. 903 (2007).

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[6] In 2009, biopharmaceutical companies spent over $5 billion in research and development activities directed towards companion diagnostics. *Id.* at 85-86. Roche and Abbott spend more than $1 billion annually on developing diagnostic products and systems.

Even apart from the costs and risks involved in this area, private investors are often deterred by greater demands from regulators and insurance providers for clinical evidence demonstrating safety and effectiveness. Human Genetics Comm'n, *Intellectual Property and DNA Diagnostics: A Report of a Seminar on the Impact of DNA Patents on Diagnostic Innovation* 5-6 (Oct. 2010) ("*Intellectual Property and DNA Diagnostics*"). The FDA, for example, is increasingly requiring that diagnostic products satisfy the same clinical and pre-market criteria as those usually reserved for pharmaceuticals and medical devices. *See* FDA, *Draft Guidance* 8-10; Press Release, FDA, *FDA To Host Public Meeting on Oversight of Laboratory-Developed Tests* (June 16, 2010), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm215766.htm?sms_ss=twitter. Most insurers, including the Centers for Medicare & Medicaid Services, do not ordinarily reimburse the costs of diagnostic screening tools, and certain predictive tests are not reimbursed at all. *See The Case for Personalized Medicine* 12; HHS, *Personalized Health Care* 88. As in the biotechnology and pharmaceutical industries, there is simply no guarantee *ex ante* that investments in research and development will be recouped through a commercially viable product. *See, e.g.*, *Intellectual Property and DNA Diagnostics* 5-6; *Personalized Health Care* 85.

B. Patents On Diagnostic Tests Are Necessary To Promote Innovation And Clinical Research

In light of the costs and high risk of failure, patents are critical to promising investors the realistic possibility of a reasonable financial return from those diagnostic products that actually make it to market and pre-

venting others from simply free-riding on the discoveries they have funded. In a 2008 report on the subject, the President's Council of Advisors on Science and Technology concluded that

> The ability to obtain strong intellectual property protection through patents has been, and will continue to be, essential for pharmaceutical and biotechnology companies to make the large, high-risk R&D investments required to develop novel medical products, including genomics-based molecular diagnostics.

Priorities for Personalized Medicine 21.[7]

Indeed, there appears to be a broad consensus among regulators, industry participants, and legal commentators that patent protections are vital to creating proper incentives for clinical research in the area of personalized medicine. *See* Nat'l Research Council, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health* 20, 25 (Merrill & Mazza eds., 2006) ("Nat'l Research Council, *Reaping the Benefits*") ("intellectual property protection is essential to ... enable firms to garner the sustained investments needed for diagnostic and drug development and testing"); Toneguzzo, *Impact of Gene Patents on the Development of Molecular Diagnostics*, 5 Expert Op. Med. Diag. 273,

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[7] In March 2000, investors mistakenly interpreted statements by President Clinton and British Prime Minister Blair as announcing their intention to narrow patent protection for gene-based innovations. Although the statements were later clarified, leading American biotechnology companies lost $50 billion in aggregate shareholder value over the following two weeks. Davies, *Cracking the Genome* 205-207 (2001).

275 (2011) ("For validation of molecular diagnostics, patents are critical to incentivize the significant investment required for these activities."); Paci et al., *Impact of DNA Patents on Pharmacogenomics Research and Development: Economic and Policy Issues*, 71 Drug Dev. Res. 485, 490 (2010) (patent protections "can stimulate private investments in an underexploited field with great potential for innovation and public health"); Sung, *Alarming Challenges Facing Medical Technology Innovation*, 6 J. Bus. & Tech. L. 35, 55-56 (2011) ("Tinkering with patent eligibility ... may bring unforeseeable consequences, including the unfortunate chilling of future innovation.").[8]

For their part, Roche and Abbott filed about 350 priority patent applications in 2010 in an effort to protect their diagnostics research and development, while also timely sharing their scientific advances with the public. Roche and Abbott firmly believe that patenting their advancements is critical to their ability to continue their investments and forward planning in the diagnostic arena. *See, e.g.*, F. Hoffmann-La Roche Ltd, *Genes & Health* 45, 116 (2007), *available at* http://www.roche.com/genes_and_health.pdf.

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[8] Some commentators argue that patents are not necessary because the costs of researching, developing, and commercializing diagnostic tests are lower than those in the biopharmaceutical industry generally. *See, e.g.*, Robertson, *The Role of DNA Patents in Genetic Test Innovation and Access*, 9 Nw. J. Tech. & Intell. Prop. 377, 389-394 (2011); Sec'y's Advisory Comm. on Genetics, Health, & Soc'y, Dep't of Health & Human Servs., *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 30-35 (2010). That minority view rests on the premise that FDA and insurance providers will not subject diagnostic tests to the same level of scrutiny as pharmaceuticals and medical devices. As noted in Section II.A. above, that assumption has proven incorrect.

A ruling that novel and nonobvious diagnostic tests are ineligible for patent protection would cripple the nascent personalized medicine industry. Two decades of effort directed toward optimizing the delivery of health care through personalized medicine would be lost. Small companies and start-ups would be particularly devastated because they rely on regular infusions of capital from investors, who often insist on the availability of patent protection as a precondition to funding ongoing research and development efforts. *See, e.g.*, Biotechnology Industry Organization, *Guide to Biotechnology* 2, 77 (2008); Barfield & Calfee, *Biotechnology and the Patent System* 27 (2007); Grabowski et al., *The Market for Follow-On Biologics*, 25 Health Aff. 1291, 1299 (2006).

III. Patent Claims Directed To Diagnostic Tests Neither Harm Patients Nor Impede The Progress Of Science

A. Patents On Diagnostic Tests Do Not Pose An Obstacle To Scientific Research

Petitioners and their amici argued below that patents on diagnostic tests stifle innovation and basic scientific research. This claim is largely based on speculation, rather than sound evidence. *See* Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 Nature Biotech. 1091 (2006). The long-standing "conventional view" is precisely to the contrary: biomedical research "is more likely to be impeded by lack of access to privately held research inputs such as materials, data and know-how than by patents." Chandrasekharan et al., *Proprietary Science, Open Science and the Role of Patent Disclosure: The Case of Zinc-Finger Proteins*, 27 Nature Biotech. 140, 140 (2009).

In fact, "empirical research suggests that the fears of widespread anticommons effects that block the use of upstream discoveries have largely not materialized." Caulfield et al., 24 Nature Biotech. at 1093; *see also* Adelman & DeAngelis, *Patent Metrics*, 85 Tex. L. Rev. 1677, 1681 (2007) ("The existing empirical studies find few clear signs that the patenting of biotechnology inventions is adversely affecting biomedical innovation."); Paci, 71 Drug Dev. Res. at 485 ("recent evidence on genetic testing suggests that many of the issues might have been overestimated or overemphasized"). The Federal Trade Commission ("FTC") likewise noted that "concern previously centered on the belief that biotechnology patent protection was too strong" and "would actually obstruct commercialization of new products, thereby hindering follow-on innovation. This problem has yet to materialize." FTC, *Emerging Health Care Issues* 32 (2009) (footnote omitted).[9]

For example, in the area of molecular diagnostics, "the evidence shows that patents do not inhibit research leading to new discoveries and, in fact, may in some cases stimulate it through the disclosure of inno-

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[9] A 2005 survey of scientists involved in biomedical research found that "patenting does not seem to limit research activity significantly, particularly among those doing basic research." Walsh et al., *Patents, Material Transfers and Access to Research Inputs in Biomedical Research* 3 (Sept. 20, 2005) ("Walsh, *Patents & Access*"); *see also* Walsh et al., *View From the Bench*, 309 Science 2002 (2005). An earlier study found that patents "rarely precluded the pursuit of worthwhile projects." Walsh et al., *Working Through the Patent Problem*, 299 Science 1021, 1021 (2003) ("Walsh, *Working Through the Patent Problem*"). When requested, licenses were often available at minimal or no cost. Walsh, *Patents & Access* 17. "Thus, not only are barriers or delays rare, but costs of access for research purposes are negligible." *Id.*

vations." Toneguzzo, 5 Expert Op. Med. Diag. at 275; *see generally* Caulfield, *Human Gene Patents: Proof of Problems?* 84 Chi.-Kent L. Rev. 133, 135-139 (2009) (reviewing numerous studies and finding no evidence of constraints on research). The key barriers to the widespread adoption of personalized medicine are not the existence of patents, but the lack of clear regulatory guidelines for approval of molecular diagnostics and the failure of insurers to provide standardized coverage criteria for diagnostic testing. Toneguzzo, 5 Expert Op. Med. Diag. at 275.

B. Patents Do Not Impede Patient Access To Diagnostic Tests

Petitioners and their amici argue that patents preclude meaningful patient access to diagnostic testing, frustrate the practice of medicine, and ultimately disserve the public interest. Those are precisely the types of concerns that Congress considered and rejected in broadly defining the classes of patent-eligible subject matter. *See, e.g.*, *Eli Lilly & Co.* v. *Premo Pharm. Labs., Inc.*, 630 F.2d 120, 138 (3d Cir. 1980) ("Congress has determined that it is better for the nation in the long-run to afford the inventors of novel, useful, and nonobvious products short-term monopolies on such products[.]").

Once an invention has been discovered and the manner of its operation disclosed to the world, it is facile to argue that the public would be better off if the invention were not patented. That ignores the critical antecedent question: would that invention exist if it were unpatentable? In the area of diagnostics, and personalized molecular diagnostics in particular, the answer is often "no." Absent patent protection, there would be little or no incentive for diagnostics compa-

nies to complete any existing projects, disclose discovered correlations between biomarkers and health-related traits, or bring any additional products to market. Sacrificing incentives for patient access runs the serious risk that patients may not have anything to access.

In any event, the evidence adduced by the petitioners and their amici is, at best, inconclusive. *See* Caulfield, 84 Chi.-Kent L. Rev. at 139-141 (concluding that "the studies available are relatively few in number and of limited methodological strength"). Patents appear to have little, if any, monopolistic effect on the price of diagnostic tests. *See* Cook-Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 Genetics Med. S15, S23-24 (2010). And it is well known that market exclusivity through patent protection creates strong incentives for advertising efforts that educate patients and health professionals who are interested in purchasing the end product. *See generally* Donohue et al., *A Decade of Direct-to-Consumer Advertising of Prescription Drugs*, 357 New Eng. J. Med. 673, 680 (2007). As with pharmaceuticals and medical devices generally, the incentive to inform the public about patented diagnostic products creates a social benefit by improving access and creating awareness among at-risk individuals. Cook-Deegan, 12 Genetics Med. at S32; *see also Sorrell* v. *IMS Health Inc.*, 131 S. Ct. 2653, 2670 (2011) (describing the "benign and, many would say, beneficial speech of pharmaceutical marketing").

To the extent there are any legitimate issues of patient access, those issues are best resolved through market-driven approaches, such as patent pools and

patent clearinghouses, rather than the blunt instrument of a blanket declaration of patent ineligibility. Stakeholders in the personalized medicine industry should be permitted to explore such collaborative licensing arrangements, which have succeeded in alleviating perceived barriers to entry and access in other industries. *See* Verbeure et al., *Patent Pools and Diagnostic Testing*, 24 Trends in Biotech. 115, 118 (2006); Ebersole et al., *Patent Pools as a Solution to the Licensing Problems of Diagnostic Genetics*, 17 Intell. Prop. & Tech. L.J. 1, 8 (2005); Toneguzzo, 5 Expert Op. Med. Diag. at 275.

C. "Rational Forbearance" Against Researchers And Medical Practitioners Is The Industry Norm

Petitioners and their amici have raised concerns of infringement suits against doctors and researchers and of patents directed to obvious common sense. *E.g.*, Pet. 29-30 (asserting that diagnostic patents "prevent medical researchers and providers from thinking about ... correlations in different ways"); AARP Cert. Br. 5 (hypothesizing patents on correlating "being a woman with an increased risk of becoming pregnant, and being elderly with an increased risk of suffering from Alzheimer's disease"). These fears are as misplaced as they are hyperbolic.

Patent holders in the biopharmaceutical industry are generally loath to threaten enforcement against the scientific and medical communities. Pressman et al., *The Licensing of DNA Patents by Large U.S. Academic Institutions: An Empirical Survey*, 24 Nature Biotech. 31, 37 (2006); Mossinghoff, *Remedies Under Patents on Medical and Surgical Procedures*, 78 J. Pat. & Trademark Off. Soc'y 789, 796-797 (1996). "Rational forbear-

ance" from patent enforcement against non-commercial and/or non-competitive uses of patented technologies has become an industry norm that plays "a significant role in ensuring the broad use of many genomic technologies." Fore Jr. et al., *The Effects of Business Practices, Licensing, and Intellectual Property on Development and Dissemination of the Polymerase Chain Reaction: Case Study*, 1 J. Biomed. Discovery & Collaboration 7, 16 (2006); *see also* Nat'l Research Council, *Reaping the Benefits* 121-122. Roche, for example, has a long-standing policy of licensing its patented diagnostic technologies at little or no cost for research purposes. Fore, 1 J. Biomed. Discovery & Collaboration at 10 (noting that Roche's stance with respect to non-commercial use of diagnostic patents was "in line with the traditional corporate practice of 'rational forbearance'"). Abbott similarly cooperates with researchers and innovators to support their important work.

Patent holders are reluctant to upset the norm of open access in the research and medical communities for fear of losing reciprocal privileges to materials and information. *See* Walsh, *Working Through the Patent Problem* 1021. Experimental and clinical uses are likely to benefit patent holders by increasing the value of patented technologies. Putative infringers in the academic and medical communities are, therefore, often viewed as prospective partners in the development of the technology. *Id.*; Pressman, 24 Nature Biotech. at 37.

Patent holders, moreover, have little or no incentive to pursue costly litigation or licensing efforts. In the context of non-commercial or non-competitive uses of patented technologies, the amount of damages at stake is not likely to justify incurring the risk of patent invalidation and the negative publicity associated with an infringement suit.

The biopharmaceutical industry thus has strong incentives not to impede research and medical uses of patented diagnostic technologies, but rather to continue the dissemination of patented diagnostic tools and methods. There is no reason to believe that diagnostic method patents will have a future effect that is any different from their effect in the past: encouraging investment in personalized medicine and other breakthrough techniques for the benefit of patients and health care generally without posing any significant burden on research. The Court should not rewrite the law of patent eligibility based on strongly-worded accusations that are not supported by the empirical evidence.

D. Concerns About The Impact On Basic Research And Patients Have Been, And Should Continue To Be, Addressed By Congress

Rather than amending section 101 to limit the scope of patent-eligible subject matter, Congress has enacted certain liability exceptions to address the very concerns raised by the petitioners and their amici. For instance, 35 U.S.C. § 271(e)(1) provides significant protections to researchers:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

In *Merck KGaA* v. *Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005), this Court held that this statutory research exception is broad enough to encompass even *commercial* research activities as to which there is a reasonable

basis to believe that the research will produce the types of information relevant to a regulatory filing. *Id.* at 206-208. Basic research for non-commercial purposes continues to be protected under the common law research exception. *See Whittemore* v. *Cutter*, 29 F. Cas. 1120, 1121 (C.C.D. Mass. 1813) (No. 17,600) (Story, J.); *see also Madey* v. *Duke Univ.*, 307 F.3d 1351, 1355 n.3 (Fed. Cir. 2002); *Deuterium Corp.* v. *United States*, 19 Cl. Ct. 624, 632 n.14 (1990).

Similarly, arguments directed to perceived limitations on clinical use and patient access have little merit in light of 35 U.S.C. § 287(c)(1), which provides,

> With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b) of this title, the provisions of sections 281, 283, 284, and 285 of this title shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity.

That limitation on remedies was enacted specifically to address the concern that patents on medical methods could unduly restrict the practice of medicine and adversely affect public health. *See* H.R. Rep. No. 104-863, pt. 7, § 616 (1996); *see also* Mossinghoff, 78 J. Pat. & Trademark Off. Soc'y at 795 n.17. Notably, Congress did not extend the immunity to "the provision of ... clinical laboratory services," 35 U.S.C. § 287(c)(3), "the practice of a patented use of a composition of matter in violation of [a] patent," or "the practice of a process in violation of a biotechnology patent," *id.* § 287(c)(2)(A).

To the extent a different balance is to be struck, the prerogative lies with Congress. This Court should, as it has in the past, refrain from crafting judicial limitations on patent-eligible subject matter based on an-

ecdotal evidence. *See, e.g.*, *Diamond* v. *Chakrabarty*, 447 U.S. 303, 316-317 (1980) (ignoring the "potential hazards in considering whether respondent's invention is patentable subject matter"). The political branches are uniquely suited to making informed compromises based on empirical evidence and careful study of the competing interests in this emerging and complex industry. *Id.* at 317 ("The choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot.").

CONCLUSION

For the foregoing reasons, Roche and Abbott respectfully submit that, in deciding the scope of patent-eligible subject matter under 35 U.S.C. § 101, the Court should consider the importance of patent protection in the personalized medicine industry and the serious adverse consequences of invalidating patents directed to the inventive features of diagnostic tests.

Respectfully submitted.

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AMICUS CURIAE BRIEF

RECORD
AND
BRIEFS

No. 10-1150

IN THE

Supreme Court of the United States

MAYO COLLABORATIVE SERVICES
(D/B/A MAYO MEDICAL LABORATORIES),
AND MAYO CLINIC ROCHESTER,
Petitioners,

v.

PROMETHEUS LABORATORIES, INC.,
Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF SAP AMERICA, INC. *AS AMICUS CURIAE* IN SUPPORT OF AFFIRMING THE FEDERAL CIRCUIT'S OPINION

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IN THE

Supreme Court of the United States

No. 10-1150

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Respondent.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF SAP AMERICA, INC. AS *AMICUS CURIAE* IN SUPPORT OF AFFIRMING THE FEDERAL CIRCUIT'S OPINION

STATEMENT OF INTEREST [1]

Amicus SAP America, Inc. is a leading technology company focused on developing innovative software

[1] Pursuant to Supreme Court Rule 37.6, counsel for amici represent that no counsel for a party authored this brief in whole or in part and that none of the parties or their counsel, nor any other person or entity other than amici or its counsel, made a monetary contribution intended to fund the preparation or submission of this brief. Pursuant to Rule 37.3(a), counsel for amici represent that all parties have consented to the filing of this brief as reflected on the docket for Case No. 10-1150.

and computer-based business solutions. The Amicus conducts significant research and development and invests heavily in commercializing innovative technologies.

SUMMARY OF ARGUMENT

The software and computer industries are a vital part of today's Information Age economy and these industries depend on patent protection for growth and innovation. A decision regarding the scope of 35 U.S.C. § 101 as applied to medical diagnostic processes could have far-reaching effects in all technology areas, including software and other computer-related technologies. Amicus SAP America, Inc. respectfully cautions this Court not to disrupt patenting of software and computer technologies in the instant case. Instead, this Court should reiterate that the scope of section 101 is purposefully broad and that this threshold test for patent eligibility must remain flexible to accommodate unforeseen inventions in all technology areas.

Today's decision should encourage the lower courts and United States Patent and Trademark Office to continue to follow the broad statutory framework and existing precedent to ferret out claims to abstract ideas, laws of nature, and physical phenomena, and discourage the exclusion of claims to useful applications of those well-settled exceptions. Petitioner's invitation to introduce a "mental steps" test that would contradict precedent and result in uncertainty for computer-related inventions should also be declined.

ARGUMENT

I. WHEN CONSIDERING THE PATENT ELIGIBILITY OF MEDICAL DIAGNOSTIC PROCESSES, THIS COURT SHOULD TAKE CARE NOT TO DISRUPT PATENTING OF SOFTWARE AND OTHER COMPUTER TECHNOLOGIES

Petitioners Mayo Collaborative Services and Mayo Clinic Rochester ("Mayo") argue against the patent eligibility of claims related to medical diagnostic methods. Amicus SAP America, Inc. ("SAP") respectfully notes that any opinion regarding the scope of 35 U.S.C. § 101 could also impact the software and computer industries that rely on process claims to protect their innovations. A flexible analysis is necessary under section 101 to avoid excluding "emerging technologies" such as software from patent eligibility. *See Bilski v. Kappos*, 130 S. Ct. 3218, 3227 (2010) ("In the course of applying the machine-or-transformation test to emerging technologies, courts may pose questions of such intricacy and refinement that they risk obscuring the larger object of securing patents for valuable inventions . . . .").

A. While the present case does not involve software, any interpretation of section 101 should avoid disrupting innovation in cutting edge technologies, including software.

Software is vital to the "Information Age" economy. In 2010, the value added to the gross domestic product ("GDP") by "Information-communications-technology-producing industries" was $684.1 billion, or 4.7% of the total GDP. Annual Report on Gross

Domestic Product by Industry, U.S. Department of Commerce Bureau of Economic Analysis (Apr. 26, 2011).[2] From 2006-2010, the U.S. Patent and Trademark Office issued 10,400 patents in class 707, which is only one of the ten classes for patents related to data processing. *See Patenting in Technology Classes, Breakout By Organization*, U.S.P.T.O.[3] The list of notable companies that obtained these patents, including IBM, Microsoft, and SAP, is testament to the fact that software innovators continue to seek patent protection to further their business development efforts. *Id.*

From 2005-2010, SAP AG alone obtained 1,477 software-related patents. *Id.* (follow "ALL CLASSES" hyperlink). In that time, SAP increased its spending on research and development by nearly 30%. SAP AG, 2010 ANNUAL REPORT 87 (2011).[4] SAP recognizes the importance of continued innovation and the value of patents to strengthen its market position and contribute to its position as an industry leader. *Id.* at 94. Reliable patent protection is vital to the continued growth of the software industry, so this Court should take care not to allow this case to become a vehicle to restrict software patenting.

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[2] http://www.bea.gov/iTable/index_industry.cfm (follow "Begin using the data" hyperlink; select "GDP-by-industry accounts"; click "Next Step"; select "Value Added by Industry") ("Information-communications-technology-producing industries" includes "computer and electronic products; publishing industries (includes software); information and data processing services; and computer systems design and related services.") (last visited Nov. 3, 2011).

[3] http://www.uspto.gov/web/offices/ac/ido/oeip/taf/tecasg/classes.htm (last visited Nov. 2, 2011).

[4] *available at* http://www.sap.com/corporateen/investors/reports/annualreport/2010/pdf/SAP_2010_Annual_Report.pdf.

B. Section 101 is purposefully broad to encourage innovation in cutting edge technologies, including software and other computer technologies.

"Section 101 is a 'dynamic provision designed to encompass new and unforeseen inventions.'" *Bilski*, 130 S. Ct. at 2337 (quoting *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 135 (2001)). Categorical rules should not be espoused that would contrast with Congress's intent to accommodate the ever-changing world of technology. *See id.* ("A categorical rule denying patent protection for 'inventions in areas not contemplated by Congress . . . would frustrate the purposes of the patent law.'" (quoting *Diamond v. Chakrabarty*, 447 U.S. 303, 315 (1980))).

Software is among the technologies eligible for patenting. In *Diamond v. Diehr*, this Court noted the Patent Office's mistaken belief that "claims that are carried out by a computer under control of a stored program constituted nonstatutory subject matter under this Court's decision in *Gottschalk v. Benson*, [409 U.S. 63 (1972)]." 450 U.S. 175, 180 (1981). Instead, "[a] claim drawn to subject matter otherwise statutory does not become nonstatutory simply because it uses a mathematical formula, computer program, or digital computer." *Id.* at 187. More recently, members of this Court cited computer programs as an example of patentable inventions that were once thought, wrongly, to be excluded from patenting. *Bilski*, 130 S. Ct. at 3227.

Noting that "[t]he digital computer may be considered by some the greatest invention of the twentieth century," the Federal Circuit recently wrote that "both this court and the Patent Office have long acknowledged that 'improvements thereof' through

interchangeable software or hardware enhancements deserve patent protection." *Ultramercial, LLC v. Hulu, LLC*, 657 F.3d 1323, 1329 (Fed. Cir. 2011). This view is consistent with the plain language of the Patent Act, which provides that patentable processes include "a new use of a known process, machine, manufacture, composition of matter, or material." 35 U.S.C. § 100(b) (2006). Because software installed on a general purpose computer puts the computer to new use, it falls squarely within the scope of subject matter eligible for patenting. *See, e.g., In re Alappat*, 33 F.3d 1526, 1545 (Fed. Cir. 1994) (en banc).

II. THE FEDERAL CIRCUIT HAS THE TOOLS NEEDED TO EVALUATE PATENT ELIGIBILITY, AND THIS COURT SHOULD RESIST INVITATIONS TO FURTHER RESTRICT SECTION 101

A. Section 101 is broad, with only three limited exceptions.

Rigid tests for patent eligibility are unnecessary and do not serve the Patent Act's purpose. For example, several members of this Court have questioned the value of the machine-or-transformation test for inventions in the Information Age, including medical diagnostic methods and software. *Bilski*, 130 S. Ct. at 3227-28. Indeed, "new technologies may call for new inquiries" to avoid "'freez[ing] process patents to old technologies, leaving no room for the revelations of the new, onrushing technology . . . .'" *Id.* at 3228 (quoting *Benson*, 409 U.S. at 71).

Rather than adopting a rigid test, *Bilski* reiterated that section 101 has only three limited exceptions, *i.e.*, laws of nature, physical phenomena, and abstract ideas. *Id.* at 3225. These exceptions "have defined

the reach of the statute as a matter of statutory *stare decisis* going back 150 years." *Id.* While encouraging the Federal Circuit to continue its efforts to devise ways to prevent patenting of these fundamental principles, this Court emphasized that the existence of three exceptions does not "give[] the Judiciary *carte blanche* to impose other limitations that are inconsistent with the text and the statute's purpose and design." *Id.* at 3226.

B. The Federal Circuit has the tools necessary to find the appropriate boundaries for patent eligible subject matter.

Courts face a difficult task when evaluating patent eligibility of innovations in the Information Age. "In searching for a limiting principle, this Court's precedents on the unpatentability of abstract ideas provide useful tools." *Id.* at 3229. The Federal Circuit is the appropriate venue to determine the contours of unpatentable abstract ideas, and it has risen to that challenge in several recent decisions. In the instant case, the Federal Circuit recognized that this Court "declined to adopt any categorical rules outside the well-established exceptions for laws of nature, physical phenomena, and abstract ideas . . . ." *Prometheus Labs. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1352 (Fed. Cir. 2010). In other recent decisions, the Federal Circuit has carefully followed this Court's guidance in evaluating patent eligibility of Information Age inventions, so this Court should allow the Federal Circuit to continue its work and refrain from imposing further restrictions.

In its first post-*Bilski* consideration of section 101 and computer technologies, the Federal Circuit noted,

"the Supreme Court in *Bilski* refocused this court's inquiry into processes on the question of whether the subject matter of the invention is abstract." *Research Corp. Techs. v. Microsoft Corp.*, 627 F.3d 859, 868 (Fed. Cir. 2010). The Federal Circuit noted this Court's forbearance from establishing "a rigid formula or definition for abstractness." *Id.* Following this Court's lead, the Federal Circuit also did "not presume to define 'abstract' beyond the recognition that this disqualifying characteristic should exhibit itself so manifestly as to override the broad statutory categories of eligible subject matter and the statutory context that directs primary attention on the patentability criteria of the rest of the Patent Act." *Id.*

Lower courts are instructed to look to the "guideposts" of *Diehr*, *Benson*, and *Parker v. Flook*, 437 U.S. 584 (1978) to identify patent-eligible processes that are not abstract ideas or natural phenomena. *Bilski*, 130 S. Ct at 3231. To analyze patentability of a process that included algorithms for halftoning digital images, the Federal Circuit applied this Court's reasoning from *Diehr*, observing that the patentees "do not seek to patent a mathematical formula" but recognized that "[i]nstead, they seek patent protection for a process of halftoning in computer applications." *Research Corp.*, 627 F.3d at 869 (citing *Diehr*, 450 U.S. at 187). Because "[t]he invention presents functional and palpable applications in the field of computer technology," the Federal Circuit concluded that the claims at issue were patent eligible. *Id.* at 868-69. The Federal Circuit reasoned that "inventions with specific applications or improvements to technologies in the marketplace are not likely to be so abstract that they override the statutory language and framework of the Patent Act." *Id.* at 869. Such

reasoning demonstrates appropriate analysis for Information Age technologies, and any ruling on Respondent's claims should not disrupt this analysis for computer-related inventions.

In *Ultramercial, LLC v. Hulu, LLC*, the Federal Circuit noted that "members of the Supreme Court and this court have recognized the difficulty of providing a precise formula or definition for the judge-made ineligible category of abstractness." 657 F.3d at 1327. The Federal Circuit again declined to craft a precise definition of abstractness, instead applying the "guidepost" cases which recognized that "[a]lthough abstract principles are not eligible for patent protection, an application of an abstract idea may well be deserving of patent protection." *Id.* (discussing *Benson*, *Flook*, and *Diehr*). Applying these cases to evaluate the claimed method for monetizing and distributing copyrighted products over the Internet, the Federal Circuit concluded that the patent "does not simply claim the age-old idea that advertising can serve as currency," but "[i]nstead the . . . patent discloses a practical application of this idea." *Id.* at 1328. The Federal Circuit also confirmed that claim breadth or a lack of specificity in a process claim is not the focus of § 101, but rather "written description and enablement are conditions for patentability that title 35 sets 'wholly apart from whether the invention falls into a category of statutory subject matter.'" *Id.* at 1329 (quoting *Diehr*, 450 U.S. at 190).

In *Ultramercial*, the Federal Circuit also dispelled the notion that computer software programming deserves no patent protection or "in the confusing terminology of machines and physical transformations, fails to satisfy the 'particular machine' requirement." *Id.* at 1328. The Federal Circuit noted its own long-

standing en banc precedent that "programming creates a new machine, because a general purpose computer in effect becomes a special purpose computer once it is programmed to perform particular functions pursuant to instructions from program software." *Id.* at 1329 (quoting *Alappat*, 33 F.3d at 1545). "Far from abstract, advances in computer technology—both hardware and software—drive innovation in every area of scientific and technical endeavor." *Id.*

In *Classen Immunotherapies, Inc. v. Biogen IDEC*, Nos. 2006-1634, 2006-1649, 2011 WL 3835409, at *1 (Fed. Cir. Aug. 31, 2011), the Federal Circuit noted:

> The § 101 patent-eligibility inquiry is only a threshold test. Even if an invention qualifies as a process, machine, manufacture, or composition of matter, in order to receive the Patent Act's protection the claimed invention must also satisfy "the conditions and requirements of this title." § 101. Those requirements include that the invention be novel, see § 102, nonobvious, see § 103, and fully and particularly described, see § 112.

Id. at *6 (quoting *Bilski*, 130 S. Ct. at 3225). Following this Court's caution that "[t]he question therefore of whether a particular invention is novel is 'wholly apart from whether the invention falls into a category of statutory subject matter,'" the Federal Circuit found some of Classen's claims passed the threshold of § 101 despite concerns about their ultimate validity. *Id.* (quoting *Diehr*, 450 U.S. at 189-190).

Regarding patent-eligibility of a process involving a law of nature or abstract idea, the Federal Circuit noted that "[i]t is now commonplace that an *applica-*

tion of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection" *Id.* (quoting *Diehr*, 450 U.S. at 187) (emphasis in original). Because only "manifestly" abstract inventions fail to pass the "coarse eligibility filter" of section 101, the Federal Circuit ruled that some of the claims that included the physical step of immunization on a determined schedule satisfied section 101. *Id.* at *8. In doing so, the Federal Circuit demonstrated its understanding of this Court's guidance that "'[r]ather than adopting categorical rules that might have wide-ranging and unforeseen impacts,' exclusions from patent-eligibility should be applied 'narrowly.'" *Id.* (quoting *Bilski*, 130 S. Ct. at 3229).

As exemplified by its recent decisions, the Federal Circuit understands this Court's guidance regarding the scope of patent eligible subject matter, and any decision in the instant case should maintain an emphasis on a broad and flexible framework for analyzing today's cutting-edge inventions under section 101, leaving the Federal Circuit to continue its work without further restriction.

C. This Court should decline Petitioners' invitation to introduce a "mental steps" test for patent-eligibility.

Petitioners suggest that the Prometheus claims contain "mental steps" and should therefore not be patent eligible. *See, e.g.*, Pet. Br. at 6 (stating that Prometheus's patent claims "broadly encompass the mental recognition of the correlations"); *id.* at 19, 33 (arguing that "Prometheus's claims culminate with [an] "open-ended 'mental step'"); Pet. for Cert. at 26 (stating that the Federal Circuit "cobble[d]

together two well-known preliminary steps . . . . and attach[ed] them to an admittedly insufficient mental step, to create a sprawling monopoly for Prometheus."). A new test excluding claim elements that encompass "mental steps" from patent eligibility is inconsistent with the plain language of the statute and this Court's precedent. *Bilski*, 130 S. Ct. at 3227 (rejecting a "categorical rule denying patent protection for 'inventions in areas not contemplated by Congress'" (quoting *Chakrabarty*, 447 U.S. at 315)).

Furthermore, Prometheus's claims are not purely mental steps. All of the claim steps are critical to the analysis of the claim as a whole under § 101, and dissecting the claims into well-known and "new" elements impermissibly entangles the threshold § 101 analysis with a § 102 novelty analysis. *Diehr*, 450 U.S. at 188 ("It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis."); *id.* at 190 ("The question therefore of whether a particular invention is novel is 'wholly apart from whether the invention falls into a category of statutory subject matter.'" (quoting *In re Bergy*, 596 F.2d 952, 961 (C.C.P.A. 1979))). To the extent that Mayo encourages the application of a "mental steps" test, this Court should reaffirm that practical applications of abstract ideas are patent eligible.

As Respondent Prometheus points out, Mayo's proposed mental steps test is ill-suited for "today's information age" and would introduce uncertainty across technologies. Resp. Br. at 34-36. Applying a mental steps test to determine whether and when software is sufficiently physical would put software claims on uncertain grounds, and is contrary to the principle that patent law should afford certainty to

patentees. *Bilski*, 130 S. Ct. at 3231 (Stevens, J., concurring) ("In the area of patents, it is especially important that the law remain stable and clear.").

CONCLUSION

For the foregoing reasons, SAP urges this Court to affirm the Federal Circuit's opinion, allowing 35 U.S.C. § 101 to remain broad to accommodate unforeseen inventions in all technology areas, to avoid disruption of software patents, and to reject any invitation to introduce a "mental steps" test for patent eligibility.

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AMICUS CURIAE BRIEF

RECORD
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On Writ of Certiorari
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INTEREST OF *AMICI CURIAE*[1]

Amici curiae Verizon Communications Inc. and Hewlett-Packard Company are leading providers of high technology products and services, whose businesses – like those of many firms in the information services, communications, and electronic technological fields – depend on, make, and sell systems and devices that incorporate a large number of components and perform a variety of functions. As such, Verizon and HP must frequently defend against meritless allegations of patent infringement. Verizon and HP also each own large patent portfolios, reflecting their roles as leading innovators in the fields of information technology and communications. As both owners of intellectual property and targets of meritless patent litigation, Verizon and HP have strong interests in a patent system that rewards rather than impedes innovation.

While *amici* have no distinctive interest in the medicine-specific issues in this case, they have a strong interest in seeing that the Patent Act of 1952, 35 U.S.C. § 1 *et seq.* ("Patent Act" or "1952 Act"), is properly interpreted and enforced. The patentable-subject-matter requirement of Section 101 must be interpreted in light of the other sections of the Patent Act, which ensure that patents are limited to concrete structures or processes that are new and

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[1] Pursuant to Supreme Court Rule 37.6, counsel for *amici* represent that no counsel for a party authored this brief in whole or in part and that none of the parties or their counsel, nor any other person or entity other than *amici* or their counsel, made a monetary contribution intended to fund the preparation or submission of this brief. Pursuant to Rule 37.3(a), counsel for *amici* represent that all parties have consented to the filing of this brief and that letters reflecting their consent are on file with the Clerk.

useful and that are described and claimed properly. Insisting that patents be circumscribed by these requirements presupposes, at the threshold, that merely adding a recognition of a new property to an old process or product does not create a newly patentable invention.

STATEMENT

This case concerns the validity of certain claims of patents – Nos. 6,355,623 and 6,680,302 (the '623 and '302 patents, respectively), both asserted by Prometheus – that involve administering a drug to a patient and then determining the results through analysis of the patient's blood. The common written description of these patents, together with the petition for certiorari and the brief in opposition, clarify that the following was known in the art prior to Prometheus's patents.

Drugs, known as thiopurine drugs, are useful in treating autoimmune diseases such as Crohn's disease, but can be ineffective in low doses and damaging or fatal in high doses. As a patient metabolizes these drugs, they are converted into active metabolites, including one known as 6-thioguanine and another known as 6-methylmercaptopurine. It is possible to measure the presence of these metabolites in a patient's blood through existing tests, including high pressure liquid chromatography. Both the administration of thiopurine drugs and the measuring of the two metabolites were already known in the art.

The claimed discovery by Prometheus's inventors was a range of the 6-thioguanine level outside which, and a 6-methylmercaptopurine level above which, they believed adjustment of the drug dosage was in

order. The Federal Circuit focused on the following two claims:

> ['623 patent claim] 1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) *administering* a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
>
> (b) *determining* the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 [picomole ("pmol")] per $8x10^8$ red blood cells *indicates a need* to increase the amount of said drug subsequently administered to said subject and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells *indicates a need* to decrease the amount of said drug subsequently administered to said subject.

Pet. App. 4a (fourth emphasis added).

> ['623 patent claim] 46. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> (a) *determining* the level of 6-thioguanine or 6-methylmercaptopurine in a subject administered a drug selected from the group consisting of 6-mercaptopurine, azathiop[u]rine, 6-thioguanine, and 6-methyl-

> mercaptoriboside, said subject having said immune-mediated gastrointestinal disorder,
>
> wherein the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells *indicates a need* to increase the[] amount of said drug subsequently administered to said subject, and
>
> wherein the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells or a level of 6-methylmercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells *indicates a need* to decrease the amount of said drug subsequently administered to said subject.

Id. at 4a-5a (third emphasis added, alterations in original).

The Federal Circuit noted that claim 1 of the '302 patent is similar to claim 1 of the '623 patent, except that it covers the 6-methylmercaptopurine metabolite as well as the 6-thioguanine metabolite. *See id.* It noted, too, that, whereas claim 1 requires administering and determining, claim 46 of the '623 patent omits the administering step. *See id.*

The Federal Circuit held that these patents covered patentable subject matter under 35 U.S.C. § 101. The court rested that holding centrally on the conclusion that both the administering and the determining steps involve physical transformations (of a patient's body and of drawn blood) and therefore so did the process as a whole. *See* Pet. App. 15a-22a. In the court's view, it was accordingly immaterial for the purposes of an analysis under Section 101 that the final "wherein" clauses, as construed, involve no more than the "mental steps" of recognizing the inventors' claimed correlation

between certain metabolite levels and toxicity or efficacy of the drug. *Id.* at 21a-22a. The court did not require any actual "upward or downward adjustment" of the drug based on that recognition. *Id.* at 22a-23a.

INTRODUCTION AND SUMMARY OF ARGUMENT

As articulated by the appellate court, this case raises a Section 101 question about the fundamental boundaries separating what may and may not be patented. The Federal Circuit relied simply on the "transformation" required by certain components of the claimed processes as sufficient to make the claims patentable under Section 101. Mayo criticizes that approach as improperly allowing a patent on the natural correlation between the concentration of certain chemicals (the two drug metabolites at issue) and toxicity and efficacy in human bodies, covering anything at all a doctor might do with recognition of that correlation once a particular patient's metabolite levels are determined (an old process).

The case should be decided on the uncontested premise that there was nothing novel about either the "administering" or the "determining" step, or the two steps taken together, and that the "wherein" clauses add only a mental step. It is longstanding law that a claim is non-patentable if it recites a prior art process and adds only the mental recognition of a newly discovered property of that process. That principle applies here and readily decides the case.

The principle is soundly based on Section 101's limitation to processes and products that are not only "useful" but "new." Even if what qualifies as "new" is understood as defined by the standards of

Section 102, it remains the case that Section 101 limits patents to what is "new." Indeed, the importance of the principle is reflected in the fact that it is intertwined with and reinforced by other principles of the Act, found in Sections 101 and 112. *See, e.g., In re Prater*, 415 F.2d 1393, 1398-99, 1401-02 (C.C.P.A. 1969) (noting both that mental processes were unpatentable before the 1952 Act and that, after the 1952 Act, the Patent and Trademark Office had considered that bar as involving Sections 101, 102, and 112). And the principle is also at least closely related to, or an application of, the "subject matter" standard of Section 101, under which certain additions to unpatentable subject matter are not enough to transform the idea into patentable subject matter. Regardless, given the language of the claims and their construction below, there is no record impediment to deciding the case on this basis.

Reaffirming this principle in the context of other patent doctrines ensures that the courts will continue to limit patents to their proper scope. Specifically, the limitations imposed by Section 101 must be understood in the context of the Patent Act's other overlapping restrictions on acceptable claims. For example, the Court has long forbidden the claiming of results, rather than the solutions for achieving results. Similarly, the Court has forbidden the use of functional claiming at the point of an invention's novelty over the prior art. These and other established doctrines (such as the requirement that the full scope of a claim be enabled) reflect a common theme – that a patent should be limited to concrete things or ways of doing things.

New knowledge by itself is often useful, but that is not enough: newly discovered laws of nature often

fit that bill. What becomes patentable is the translation of such new knowledge into a concrete structure or process that is new and useful and described and claimed properly. The principles insisting that patent claims be limited to that kind of contribution presuppose, at the threshold, that merely adding a recognition of a new property to an old process or product does not create a newly patentable invention. This Court has squarely recognized those principles previously in a line of cases, including *General Electric Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242 (1945); it should reaffirm them in the current case.

ARGUMENT

I. THE PATENT ACT DOES NOT ALLOW A CLAIM THAT ADDS TO AN OLD PROCESS ONLY A MENTAL RECOGNITION OF A NEWLY DISCOVERED PROPERTY OF THAT PROCESS

The claims in this case are invalid because they recite an old process to which is added only a mental step recognizing a property of that process, and such recognition does not make an old process new.

As described above, the patent claims recite only the steps of administering a drug and determining certain metabolite levels, followed by "wherein" clauses saying that certain levels "indicate" a possible meaning of certain levels for patient health. But as relevant here, Section 101 limits patentable subject matter to "any new and useful process." In this case, there is no "new and useful process."

As Mayo has stated, and as Prometheus has not disputed, the combination of administering the drug and determining the level of the two metabolites, specifically for patients with the immune-mediated

gastrointestinal disorders recited in the claim preambles, is an old process.[2] The remaining portions of the claims consist of "wherein" clauses, but these clauses prescribe no additional physical actions at all. Their language does not even purport to do so: they merely recite that certain metabolite levels (the result of the determining step) have a certain significance for health. That can be important information, but there is no recitation of an additional non-mental step. Indeed, while the district court initially stated that it read the clauses to provide for a "'warning,'" Pet. App. 6a (quoting district court), it clarified that it did not mean that a step of actually issuing a statement to others was required. Rather, this was a purely "'mental step'" of recognizing the possible health significance of the result of the determining step – a property of the (administering and) determining process. *Id.* at 7a (quoting district court). And the Federal Circuit expressly agreed that the "wherein" clauses recited only a "mental step." *Id.* at 21a, 22a-23a.

This property-recognition step is not enough to turn the prior art process into a "new and useful process" under Section 101. Indeed, the Federal Circuit itself purported to recognize that the mental step of the "wherein" clauses was not "patent-eligible." *Id.* at 21a. More importantly, this Court's

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[2] Mayo's petition repeatedly asserted that the administering and determining steps, even together, were old. *See* Pet. 5, 24, 26. Prometheus was careful in its brief in opposition never to take issue with that assertion. *See* Br. in Opp. 3-5, 14-15, 16-18. For that reason, and because the Federal Circuit decided the case on this premise as well, Mayo's premise may be accepted by this Court. *See* Sup. Ct. R. 15.2 (where respondent does not contest facts asserted in petition, Court may accept such facts as defining the question to be decided).

precedent squarely establishes that mere recognition of a property of an old process (or product) does not create a patentable new process (or product).

In *General Electric Co. v. Jewel Incandescent Lamp Co.*, 326 U.S. 242 (1945), the plaintiff had a patent that related to frosted glass light bulbs, in which the interior of the bulb was frosted to reduce glare without severely reducing light output. *See id.* at 243-44. The patentee recognized that multiple etchings would round out the sharp crevices of the first etching of the glass, thereby increasing light output and making the glass stronger. *See id.* at 246. The prior art disclosed such multiple etchings of the inside of a bulb, but did not recognize that this would create stronger glass. *See id.* at 246-47. The Court held that the patent was invalid because "the prior art discloses the method of making an article having the characteristics of the patented product, though all the advantageous properties of the product had not been fully appreciated." *Id.* at 248. The Court stated that "[i]t is not invention to perceive that the product which others had discovered had qualities they failed to detect." *Id.* at 249.

Nor does *Jewel Incandescent* stand alone on this point. In *Ansonia Brass & Copper Co. v. Electrical Supply Co.*, 144 U.S. 11 (1892), the patent at issue was on insulation for electrical wires, where the patentee discovered that an old form of insulation was also non-combustible. *See id.* at 14. The patentee argued that the patent claims to a non-combustible insulation were valid because, previously, that insulation "was not intended to be, and perhaps was not known to be, incombustible." *Id.* at 17. The Court rejected this argument, holding that "nothing is better settled in this court than that the application

of an old process to a new and analogous purpose does not involve invention, even if the new result had not before been contemplated." *Id.* at 18.

The patent claims in *De Forest Radio Co. v. General Electric Co.*, 283 U.S. 664 (1931), were on vacuum tubes for radios, where the vacuum tubes were made so that there was very little gas left in the tube after production. *See id.* at 670-71. Prior to the patent, people had known that increasing the vacuum made the tubes perform better. *See id.* at 680. The patentee Langmuir argued, however, that the claims were valid because he understood and explained the scientific principle behind the efficacy of a high vacuum. *See id.* at 683. This Court rejected that argument and invalidated the patent claims, holding:

> Even if the asserted difference were established, it is no more than the scientific explanation of what . . . others knew, before Langmuir, of the effect of the high vacuum on the discharge, and the methods and devices for procuring the vacuum. It is method and device which may be patented and not the scientific explanation of their operation.

Id. at 684-85. *See also Corona Cord Tire Co. v. Dovan Chem. Corp.*, 276 U.S. 358, 369 (1928) ("Nor, on the other hand, does it minimize or affect the priority of completed discovery by some one else before [patentee] Weiss that the prior discoverer may not have perceived and stated all the advantages of an earlier use of [diphenylguanidine] as an accelerator.").

Thus, adding to the old process in Prometheus's patent claims nothing more than a mental step of recognizing the possible health (toxicity or efficacy)

significance of the result of the process does not define a "new and useful process." This is the essence of Mayo's argument. Prometheus has protested (Br. in Opp. 15, 18) that separation of claim elements into the old and the new is inappropriate under *Diamond v. Diehr*, 450 U.S. 175, 188 (1981). *See Bilski v. Kappos*, 130 S. Ct. 3218, 3230 (2010). But whatever *Diehr* ruled, it established no across-the-board bar on such claim parsing. In particular, it did not involve, and so did not address, the kind of claims at issue here – in which some claim elements add nothing but recognition of the property of other elements. *See Diehr*, 450 U.S. at 179 n.5. As to that particular type of claim, which is at issue in the current case, the principle of *Jewel Incandescent* and related precedents makes separation essential, and so the objection by Prometheus is meritless.

II. THE UNPATENTABILITY OF THE CLAIMS AT ISSUE REFLECTS FUNDAMENTAL PRINCIPLES EMBODIED THROUGHOUT THE PATENT ACT

The longstanding rule of *Jewel Incandescent* and related precedents is anything but peripheral to the core of patent law. Rather, it reflects fundamental principles that define what patent law is meant to protect and what it excludes. As discussed below, these principles are embodied not only in Section 101 but in other provisions of the patent law, as long understood by the Court.

In codifying prior patent case law in the Patent Act, Congress recognized that "Section 101 sets forth the subject matter that can be patented, 'subject to the conditions and requirements of this title.' The conditions under which a patent may be obtained follow" that provision. S. Rep. No. 82-1979,

at 5 (1952) (quoting Section 101), *reprinted in* 1952 U.S.C.C.A.N. 2394, 2399. Thus, Congress's intention was that the various principles of the Patent Act be read together in deciding when a patent is valid.

These fundamental principles perform, in overlapping and reinforcing ways, the critical function of keeping patent protection within proper bounds. Those bounds are imposed to preserve the freedom for others' investigations, innovations, and useful activities that are as important to the advancement of knowledge and progress of society as is legitimate protection for inventions. *See, e.g.*, *Bilski*, 130 S. Ct. at 3225; *id.* at 3227, 3229 (plurality); *Laboratory Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126-27 (2006) (Breyer, J., dissenting from dismissal of writ of certiorari as improvidently granted) ("Patent law seeks to avoid the dangers of overprotection just as surely as it seeks to avoid the diminished incentive to invent that underprotection can threaten.").

Whether these principles are applied robustly in practice depends vitally on this Court's guidance as to their core meaning and its emphasis on their importance. Just as the Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), set obviousness law on a more realistic and less blinkered, document-focused course, it should here reaffirm and stress the significance of a group of principles that reinforce the *Jewel Incandescent* rule. Only by reemphasizing the strength of these principles will the lower courts limit patent claims to concrete practical advances in useful technology.

A. Section 101

The Court in *Bilski* reinforced the line between unpatentable "laws of nature, physical phenomena, and abstract ideas," on one hand, and a potentially patentable "new and useful process, machine, manufacture, or composition of matter," on the other. *Bilski*, 130 S. Ct. at 3225 (internal quotation marks omitted). A common-sense way of capturing that distinction is to say that, for products (machines, manufactures, or compositions of matter), a claim must define a physical structure and, for processes, a claim must define physical actions. For the latter, that does not mean that a process must be tied to a particular machine or that it must achieve a transformation of some material. *See id.* at 3226-27. A series of physical actions may be capable of being carried out with any number of different machines; and a series of physical actions may not have the effect of transforming some material. But the natural import of the exclusion of "laws of nature, physical phenomena, and abstract ideas" is that the Section 101 category of "process" is restricted to things people physically do (with or without mechanical or other aids). *See also* 35 U.S.C. § 100(b) ("The term 'process' . . . includes a new use of a known process, machine, manufacture, composition of matter, or material."). The Federal Circuit itself recognized the exclusion of mere "mental steps." Pet. App. 21a-22a.

To preserve the import of this rule, it may not be circumvented by merely tacking onto well-known physical steps the novel mental steps recited in the patent claims at issue here. Thus, in *Gottschalk v. Benson*, 409 U.S. 63 (1972), this Court barred claims that merely added to a general-purpose digital

computer an otherwise-unpatentable mathematical algorithm. *See id.* at 64, 71-72. And in *Parker v. Flook*, 437 U.S. 584 (1978), the Court barred patenting of a procedure that consisted of taking a series of known chemical-process steps and making only one change, namely, adding reliance on a mathematical algorithm. *See id.* at 590. *See also Bilski*, 130 S. Ct. at 3230 (in *Flook*, the "only innovation was reliance on a mathematical algorithm"). "As the Court later explained, *Flook* stands for the proposition that the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment' or adding 'insignificant postsolution activity.'" *Id.* (quoting *Diehr*, 450 U.S. at 191-92).

Taken together with the *Jewel Incandescent* principle, these cases may thus be understood as reflecting this Court's more general holding that certain additions to a patent claim do not suffice to render unpatentable subject matter patentable. *See Flook*, 437 U.S. at 590 ("The notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process exalts form over substance.").

To be sure, the Court in *Diehr* subsequently "established a limitation on the principles articulated in *Benson* and *Flook*," in that it required consideration of the "invention as a whole, rather than 'dissect[ing] the claims into old and new elements and then . . . ignor[ing] the presence of the old elements in the analysis.'" *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 188) (alterations in original). The mere fact that one of the elements of the patent claim made use of a mathematical algorithm was insufficient to invalidate the claim

"because all inventions can be reduced to underlying principles of nature." *Diehr*, 450 U.S. at 189 n.12. But that "limitation" does not repudiate the results in *Benson* and *Flook* or the insufficiency of adding "insignificant postsolution activity" to otherwise-unpatentable matter – on which this Court pointedly relied in *Bilski*, 130 S. Ct. at 3230, 3231 (internal quotation marks omitted). The *Diehr* "limitation" thus leaves in place, without providing clear further definition, the principle that certain kinds of additions to otherwise-old processes are insufficient to bring a process within the subject matter covered by Section 101. The *Jewel Incandescent* principle that decides the present case may be understood as applying that rule to forbid the mere addition of a recognition of a property, a mental step, to what is otherwise, in full, an old set of steps.

The principle governing the present case is also reinforced by this Court's important decision in *Brenner v. Manson*, 383 U.S. 519 (1966), which enforced Section 101's requirement that an article or process must be not only "new" but also "useful." *See id.* at 528-32. There, this Court held invalid a patent claim to a new process for making a chemical because the patentee failed to disclose any utility for the chemical. *See id.* at 531-32. Mere identification of new knowledge – a mental step of recognizing a newly discovered fact about the world (such as the process for making a chemical) – is not enough. Thus, it is a requirement not only that a patented process be new, but also that it have a known use besides being the object of further scientific research. To allow patenting of processes or articles, without a clear explanation of their use, "creates a monopoly of knowledge" that "may confer power to block off

whole areas of scientific development." *Id.* at 534. That practical utility is required for an otherwise-patentable process or product reinforces the *Jewel Incandescent* principle that merely adding a mental step of recognizing a property does not create a newly patentable process or product that is otherwise old.

B. Section 112

The Court has long forbidden claiming of results, rather than a particular solution that achieves those results. For example, in *Le Roy v. Tatham*, 55 U.S. (14 How.) 156 (1853), the patent was based on the discovery that lead had the property that, when hot, it could be welded into pipes, rather than cast. *See id.* at 172. The Court held that this fundamental principle – the properties of lead – could not be patented. The Court's concern was that, to grant a patent on this principle rather than an application of that principle, "would prohibit all other persons from making the same thing by any means whatsoever. This, by creating monopolies, would discourage arts and manufactures, against the avowed policy of the patent laws." *Id.* at 175.

Similarly, in *O'Reilly v. Morse*, 56 U.S. (15 How.) 62 (1854), the Court rejected a patent claim "to every improvement where the motive power is the electric or galvanic current, and the result is the marking or printing intelligible characters . . . at a distance." *Id.* at 112. The Court insisted that the patent statute limits claims to the particular means described for producing the characters at a distance and forbids a claim to "an effect produced by the use of electro-magnetism distinct from the process or machinery necessary to produce it." *Id.* at 120. Precisely in order to avoid the restraint on others'

"attempting to improve upon the manner and process which [the patentee] has described," such a claim "is as strongly forbidden . . . as if some other person had invented it before him," *id.* at 120-21 – in essence the *Jewel Incandescent* principle that applies to the present case.[3]

Likewise, the Court has forbidden the use of functional claiming at the point of novelty over prior art, again insisting on limiting claims to concrete actions and structures that carry out the desired functions (leaving room for others to use or invent other means for carrying them out). In the major precedent pre-dating the 1952 Act, *Halliburton Oil Well Cementing Co. v. Walker*, 329 U.S. 1 (1946), the Court invalidated a patent claim on a device for measuring the distance of oil down a well using sound waves, explaining that "[t]he language of the claim thus describes this most crucial element in the 'new' combination in terms of what it will do rather than in terms of its own physical characteristics or its arrangement in the new combination apparatus." *Id.* at 9. Rather than describing the inventive mechanism, the patent claim recited only a "tuned acoustical means." *Id.* at 7 (internal quotation marks omitted). The Court held, following earlier precedents, that such language rendered the claim invalid because, "unless frightened from the course of experimentation by broad functional claims like these, inventive genius may evolve many more devices to accomplish the same purpose." *Id.* at 12.

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[3] The Federal Circuit has taken some steps toward implementing this limitation on claiming results, chiefly in the chemical and related fields, through the written-description requirement of Section 112. *See Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010) (en banc).

As noted, *Halliburton* built on earlier precedents. In *General Electric Co. v. Wabash Appliance Corp.*, 304 U.S. 364 (1938), the Court invalidated a patent claim on a tungsten filament for light bulbs "made up mainly of a number of comparatively large grains of such size and contour as to prevent substantial sagging." *Id.* at 368 n.1 (internal quotation marks omitted). The court of appeals had upheld the claim on the basis that it was not "'wholly' functional," but included functional limitations as part of a larger structure. *Id.* at 371 (quoting court of appeals). This Court rejected that conclusion, holding that the "vice of a functional claim exists" when the inventor "recites what has already been seen, and then uses conveniently functional language at the exact point of novelty." *Id.*

Likewise, in *Holland Furniture Co. v. Perkins Glue Co.*, 277 U.S. 245 (1928), the Court invalidated a patent claim on glue made from starch "having substantially the properties of animal glue." *Id.* at 250. The Court held that the innovative "ingredient was thus described, not in terms of its own physical characteristics or chemical properties or those of the product, but wholly in terms of the manner of use of the product," *i.e.*, as animal glue is used. *Id.* at 256. The Court explained that such functional claiming does not promote innovation because "[a] claim so broad, if allowed, would operate to enable the inventor, who has discovered that a defined type of starch answers the required purpose, to exclude others from all other types of starch, and so foreclose efforts to discover other and better types." *Id.* at 257.

Congress responded to the *Halliburton* line of cases by reinforcing the underlying insistence on limiting patents to structures and actions. Thus,

in 1952, Congress provided expressly for a patent applicant to use functional claim language but only in a way that limited the claim scope to particular structures and actions specified elsewhere in the patent. The provision, now codified as 35 U.S.C. § 112 ¶ 6, declares:

> An element in a claim . . . may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification and equivalents thereof.

Under this provision, the patent applicant may use functional language in the claim, but the prerequisite for doing so is that the applicant must detail the specific structure, material, or acts of the invention in the non-claim portion of the patent, and the claim term then is limited in its reach to those specific structures, materials, or acts or equivalent ones. *See Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997) ("Section 112, ¶ 6, now expressly allows so-called 'means' claims, with the proviso that application of the broad literal language of such claims must be limited to only those means that are 'equivalen[t]' to the actual means shown in the patent specification.") (alteration in original). The result is still that patent scope is limited to specific structures and actions (and their equivalents). The only difference is that the patent applicant now may identify such structures and actions either in the claim language *or* (under Section 112 ¶ 6) in the specification. The substantive limitation of scope to structures and actions remains.

Again, these decisions reinforce the *Jewel Incandescent* principle by addressing specific examples of additions to a patent claim that are insufficient to render unpatentable subject matter patentable. Thus, taking the prior art as a starting point and merely adding an expected result or functional element at the point of novelty cannot create a valid claim under the Patent Act. Regardless of the context in which these principles are articulated, they serve to limit the scope of claims to avoid closing off entire areas of innovation.

CONCLUSION

Amici respectfully suggest that the patent claims at issue are invalid because they merely add a mental-recognition step to an old process, which violates the related restrictions on the scope of patents imposed by the Patent Act.

Respectfully submitted,

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